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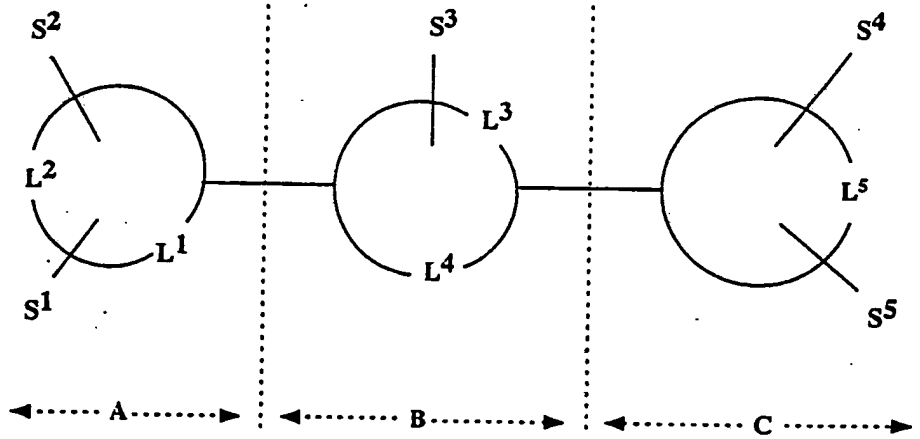

(57) Abstract

This invention relates to novel compounds with the general structure A-B-C and their pharmaceutically acceptable salts, to medicinal compositions containing them, and to the use of such medicinal compositions in the treatment of certain disease states. The compounds of the invention are represented schematically as A-B-C wherein S^1-S^4 are in general lypophilic residues, S^5 is a polar or hydrophilic residue, and L^1-L^5 are optional linking units. The compounds of this invention bind to CCK and/or gastrin receptors with high affinity and are therefore useful in the treatment of diseases which involve the dysfunction of a physiological process regulated by either of these hormones.

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CCK AND/OR GASTRIN RECEPTOR LIGANDS

This invention relates to novel compounds that bind to the CCK and/or gastrin receptor with high affinity, to processes for the preparation of these compounds, and to their use in the treatment of certain disease states.

BACKGROUND TO THE INVENTION

Cholecystokinin (CCK) and gastrin are two members of a family of peptide hormones. They were originally discovered and described as agents acting on organs of the gastrointestinal system. CCK stimulates the contraction of the gall bladder and the release of digestive enzymes from the pancreas. Gastrin stimulates the secretion of gastric acid. More recently CCK has been found in the brain, indicating that it may also act as a neurotransmitter or neuromodulator.

Both CCK and gastrin are biosynthesised as prepro-hormones. The biologically active peptides are then released after a series of post-translational modifications. In the case of CCK a number of active forms are produced which vary in the number of amino acid residues they contain. The smallest is a tetrapeptide (CCK-4) and the largest has 58 residues (CCK-58). A variety of gastrins are also known, of which the 17-residue peptide (G-17) is probably one of the most important. Additionally both CCK and gastrin have a tyrosine residue which is found as both the free phenol and as the O-sulphate. All the biologically active forms of both CCK and gastrin share a common tetrapeptide amide sequence at their C-terminus. The C-terminal sequences of the two peptides are:

. . . -Asp-Tyr*-Met-Gly-T (CCK)

. . . -Glu- Ala-Tyr*-Gly-T (Gastrin)

(Tyr* = tyrosine residue which is optionally O-sulphated; T = Trp-Met-Asp-Phe-NH_2)

Apart from its actions on the gall bladder and pancreas mentioned above CCK also influences secretion, absorption and motility in the stomach and intestines, and causes the

secretion of pancreatic hormones such as somatostatin. In the central nervous system CCK appears to be important in anxiogenesis, analgesia and appetite regulation.

Gastrin plays a fundamental part in the control of gastric acid secretion, although the precise mechanism by which this secretion is regulated remains in doubt. Gastrin causes the release of histamine from the ECL-cells in the stomach wall. Histamine then stimulates the parietal cells to secrete acid. It is possible that gastrin can directly stimulate the parietal cells, but this in particular is a point of controversy. Gastrin also increases the blood flow in the stomach wall, but this might also be an indirect effect mediated by histamine, and exerts a trophic effect on the gastric mucosa. (For a more complete review, and leading references, see ref. 1).

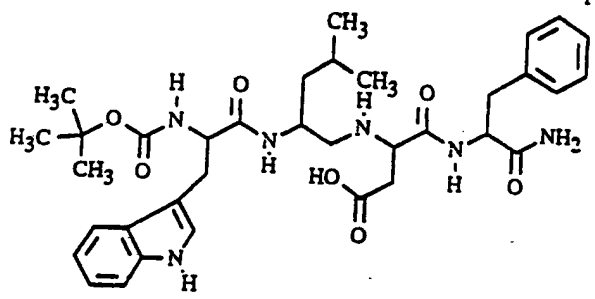
CCK and gastrin interact with their target organs through specific receptors located in the cell surface plasma membranes. It is generally agreed that there are two different CCK receptors. The CCK-A (for alimentary) type is found in the peripheral tissue, and is the receptor which mediates the actions of CCK on the pancreas, gall bladder and intestines. It is also found in certain specific brain regions, where it might be involved in the control of appetite. The CCK-B (for brain) receptor type is more widely distributed in the CNS, and is thought to be involved in anxiety and other central actions of CCK. There is only one gastrin receptor type, found particularly in the stomach wall. It appears to show very similar ligand specificity to the CCK-B receptor, and the CCK-B receptor is commonly used as a model for the less readily isolable gastrin receptor.

There is evidence that this simple classification system is incomplete. Some tissues appear to have heterogeneous CCK receptor populations, with both high and low affinity sites, and there is some variation in ligand specificity for CCK-A receptors in tissue preparations from different organs. (For more details see ref. 2).

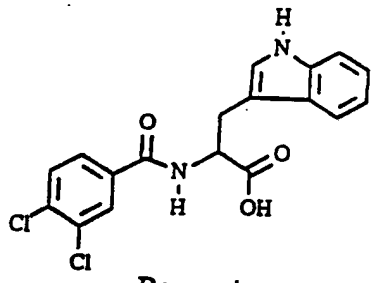
A number of approaches to the discovery of CCK and gastrin receptor agonists and antagonists have been tried and have led to the development of a wide variety of structural types as pharmacological tools for the elucidation of the function of CCK and gastrin *in vivo* and as potential drugs (see Figure).

Simple modifications to the natural peptide structures have provided peptides with unusual amino-acids as well as amides, esters and "reduced" and other pseudo-peptides.[3] A group from Abbott Laboratories has shown that conformationally restricted amino-acid surrogates can give compounds of high affinity.[4] Other studies have restricted the peptide conformation by cyclisation between two amino-acid side chains.[5]

Figure: Some Representative CCK/Gastrin Receptor Ligands



(Martinez *et al*)



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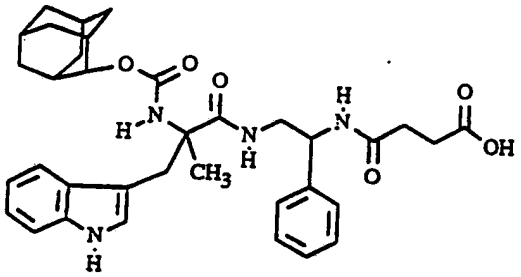

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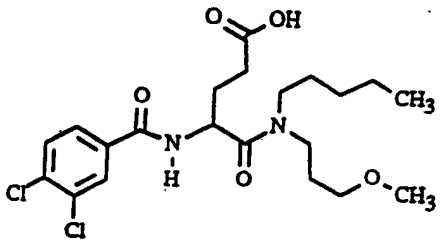

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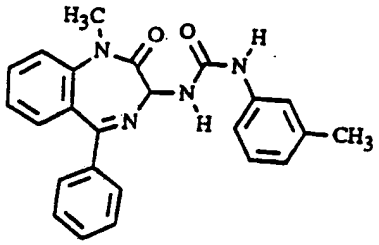

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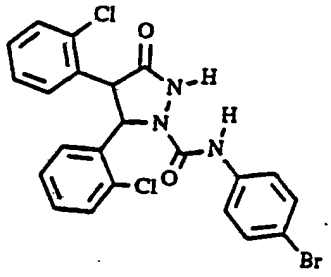

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Tryptophan derivatives have been widely explored. The earliest compounds studied, e.g. benzotript, were not very potent, but more recently disclosed compounds have

demonstrated better affinity.[6] Perhaps the best example of this development is CI-988, a tryptophan "dipeptoid" from Parke-Davis.[7]

A group from Rhone-Poulenc has disclosed a number of compounds which have some analogy with the tryptophan analogues developed by Biomeasure but which lack the indolylmethyl side chain.[8]

Aspartic and glutamic acids have also provided important compounds. Again the original modest lead, proglumide, has been overtaken by more recent developments.[9]

Microbial metabolites are a traditional source of lead structures, and a number of compounds have been shown to have affinity for the CCK-receptor.[10] Probably the most significant of these is asperlicin. It has inspired an enormous effort in the development of benzodiazepine derivatives as CCK ligands. This particular area is probably the most active single area of research into new compounds as CCK and gastrin antagonists.[11]

A group from Lilly has published its findings on a series of quinazolinones which are also inspired by the structure of asperlicin.[12]

A number of groups have disclosed compounds which can be broadly described as small heterocycles with pendant aromatic substituents.[13] These compounds may bind in a similar manner to the benzodiazepines.

Cyclic nucleotide derivatives have been known for some time to be CCK antagonists. The best is dibutyryl cyclic GMP, but its affinity for the receptor is only modest compared with other types of compound.[14]

Finally, it has been demonstrated that some peptides and their analogues, which are not themselves homologous with CCK/gastrin, have some affinity for the CCK receptor. This has been shown in analogues of substance P, calcitonin-gene-related peptide and somatostatin.[15]

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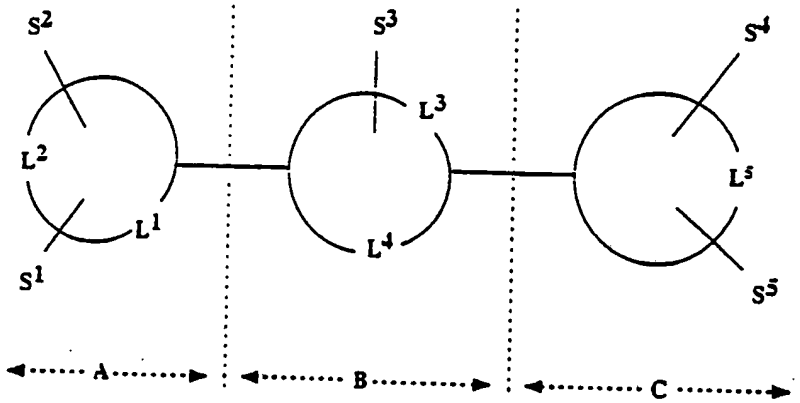
DESCRIPTION OF THE INVENTION

The compounds of the present invention are ligands with a high affinity for CCK and/or gastrin receptors. They can be represented by the general formula **A-B-C** in which **A**, **B** and **C** are subunits as defined below and are linked by covalent bonds. It is presumed that the compounds of this invention achieve their potency by mimicking the C-terminal tetrapeptide which is common to CCK and gastrin, but this is not necessarily always the case. The important features of **A**, **B** and **C** are represented schematically below as general structure **a**:



a

in which:

S^1 is an optional substituent group, but when present is a hydrophobic residue

S^2 is a mandatory substituent, and is always an aromatic (including heteroaromatic) residue

S^3 is also mandatory, and is generally a hydrophobic residue (but with the exceptions mentioned below)

S^4 is mandatory, and is a hydrophobic residue

S^5 is optional, and is generally a hydrophilic or polar residue

L^1 - L^5 are linking elements (covalent bonds or chains of atoms) which are optional with the proviso that if S^1 is present then L^2 must be present, and that at least one of L^3 and L^4 must be present.

Exceptions to the above fall into two categories:

when S^5 is absent S^3 can be a hydrophilic residue, and

when B is a group such as a proline residue then L^3 can take the place of S^3.

It is not the inventors' intention that the above be regarded as a definition of the invention. It is intended to be an aid to understanding the key features of the compounds of the invention, and it will be used below as a guide in explaining the development of the preferred embodiments of the invention. The precise scope of the invention is defined in Claim 1 below.

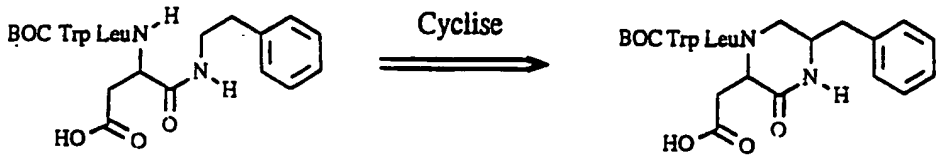
In general, then, A is a unit that can have either one or two hydrophobic residues attatched. When only one is present then it is an aromatic system, and A is a group such as (substituted)phenyl carbamoyl, indoleacetyl or isoquinolinecarbonyl. When both hydrophobic residues are present and the linking unit L^1 is absent then A mimics a blocked aromatic amino-acid such as BOC-tryptophan or benzoyl-phenylglycine. When L^1 is present then A is cyclic. The aromatic residue can either be pendant to this ring or fused to it, giving, for example, a phenylproline and an indoline respectively. In these cases S^1 can be absent or it can be any hydrophobic group, for example a BOC- or a benzoyl group.

For subunit B there are three possibilities. When L^3 is present and L^4 is absent then B is analogous to an amino-acid, or a residue that can mimic an amino-acid, such as, for example O-benzyl-threonine or its "reduced" isostere. When L^3 is absent and L^4 is present then B can be considered to be an N-alkyl amino-acid analogue. When both L^3 and L^4 are present then B is cyclic. The ring can in itself constitute the hydrophobic residue S^3, for example when B is a proline residue. Alternatively, the residue can be a pendant group or, if it is cyclic, it can be fused to the ring of B, giving for example a substituted proline or an indoline respectively.

For subunit C, if L^5 is absent then the subunit is analogous to an N-alkylated amino-acid (as was B with L^3 absent and L^4 present). In this case S^5 must be present, and mimics the backbone of the amino-acid. In some of the embodiments of the invention S^5 is extended and mimics a dipeptide chain. When L^5 is present S^5 can be absent, or if it is present it performs a function analogous to that just described. With L^5 present S^4 can either be pendant to the ring so formed, or it can be fused with it.

We have found that certain combinations of the above options lead to compounds with high affinity for the target receptors, and in some cases with high selectivity between receptor sub-types. The result of our studies is a group of novel compounds with pharmacological properties as good as, and often better than, CCK and gastrin receptor ligands previously described, which makes them useful in the treatment of certain ailments. These compounds are the basis of the present invention.

Conceptually, the compounds of the present invention are derived from the amino-acid sequence of the naturally occuring hormones. The starting point of our investigation was an amide described by Martinez *et al.* (*Int. J. Peptide Protein Res.*, 28, 529-535, 1986). We found that constraining the conformational freedom of the ester by cyclization gave compounds which retained some affinity for both CCK-A and CCK-B receptors. This key step is represented below.

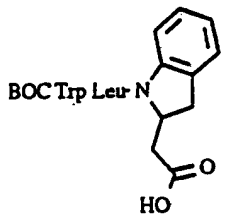


b

Comparing the structure of the cyclised compound (b) with the diagramatic representation of the compounds of this invention (a) described above shows the following set of correspondences:

S^1 = BOC
S^2 = Trp side chain
S^3 = Leu side chain
S^4 = benzyl group
S^5 = carboxymethyl group
L^1 & L^4 absent
L^2, L^3 & L^5 present.

Further investigation demonstrated that potency was improved, particularly with respect to the CCK-A receptor, if the aromatic residue in S^4 was fused to the C ring (compound c), and that the BOC-amino group could be omitted.



c

This leads to a first preferred embodiment of the present invention, defined precisely in Claims 19-20, in which:

A is a fused heteroaromatic substituted acyl residue, or an N^{α}-blocked tryptophan residue;

B is a hydrophobic amino-acid residue, or a surrogate of one;

C is a benzo-fused piperidine or pyrrolidine, further substituted with a carboxyl or carboxyalkyl residue, which can be blocked as an ester, or extended, for example, by acylating an amino-acid residue.

In particular, this preferred embodiment of the invention includes;

Ethyl (2R)-1-{*tert*-butyloxycarbonyl-tryptophanyl-leucyl}-2,3-dihydroindole-2-acetate

Ethyl (2S)-1-{(2S)-2-(*tert*-butyloxycarbonyl-tryptophanylamino)-hexanoyl}-2,3-dihydroindole-2-carboxylate

(2R)-1-{Indole-2-carbonyl-phenylalanyl}-2,3-dihydroindole-2-acetic acid

(2R)-1-{(2S)-2-(Indole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetic acid

3-{(2R)-1-{(2S)-2-(Indole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-yl}-propanic acid

(2R)-1-{(2S)-2-(5-Fluoroindole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetic acid

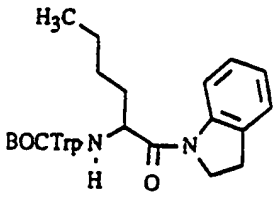
(2R)-1-{(2S)-2-(5-Chloroindole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetic acid

(3R)-2-{(2S)-2-(Indole-2-carbonylamino)-4-phenylbutanoyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

N-{(2S)-1-{(2S)-2-(Indole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetyl}-glycine

3-{(2S)-1-{(2S)-2-(Indole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-carbonylamino}-propanoic acid.

Further investigation revealed that deletion of the S^5 substituent in the compounds typified by **c** generally resulted in compounds which were more potent and selective for the CCK-A receptor (e.g. compound **d**).



d

This leads to a second preferred embodiment of the present invention, defined precisely in Claims 16-18, in which:

A is a fused heteroaromatic substituted acyl residue, or an N^{α}-blocked tryptophan residue;

B is usually a hydrophobic amino-acid residue, or a similar surrogate, but may also be a hydrophilic amino-acid residue, or a similar surrogate;

C is a benzo-fused piperidine or pyrrolidine.

In particular, this preferred embodiment of the invention includes;

1-{*tert*-Butyloxycarbonyl-tryptophanyl-leucyl}-2,3-dihydroindole

1-{(2S)-2-(*tert*-Butyloxycarbonyl-tryptophanylamino)-hexanoyl}-2,3-dihydroindole

1-{(2S)-2-(3-Indole-3-propanoylamino)-hexanoyl}-2,3-dihydroindole

1-{*tert*-Butyloxycarbonyl-tryptophanyl-phenylalanyl}-2,3-dihydroindole

1-{(2S)-2-(*tert*-Butyloxycarbonyl-tryptophanylamino)-4-phenylbutanoyl}-2,3-dihydroindole

1-{*tert*-Butyloxycarbonyl-tryptophanyl-(β-O-benzyl)-D-aspartyl}-2,3-dihydroindole

1-{*tert*-Butyloxycarbonyl-tryptophanyl-aspartyl}-2,3-dihydroindole

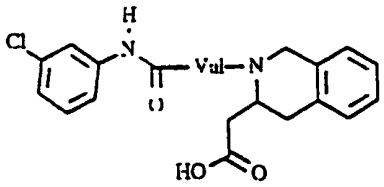
1-{*tert*-Butyloxycarbonyl-tryptophanyl-(γ-O-benzyl)-glutamyl}-2,3-dihydroindole

1-{*tert*-Butyloxycarbonyl-tryptophanyl-glutamyl}-2,3-dihydroindole

2-{*tert*-Butyloxycarbonyl-tryptophanyl-D-phenylalanyl}-1,2,3,4-tetrahydroisoquinoline

2-{(2R)-2-(*tert*-Butyloxycarbonyl-tryptophanylamino)-4-phenylbutanoyl}-1,2,3,4-tetrahydroisoquinoline.

Modifications at the **A** subunit of compounds typified by structure **c** indicated that smaller groups could be employed without incurring a loss of activity. In particular, the replacement of BOC-Trp with an arylcarbamoyl residue (as in compound **e**) resulted in compounds which had high affinity for the CCK-A and/or CCK-B/gastrin receptor sub-types.



e

This leads to a third preferred embodiment of the present invention, defined precisely in Claims 2-7, in which:

A is a substituted or unsubstituted phenylcarbamoyl residue (i.e. L^1, L^2 and S^1 are absent);

B is a hydrophobic amino-acid, or a similar surrogate;

C is a piperidine or pyrrolidine which may be benzo-fused or may have a pendant hydrophobic substituent, and which is further substituted with a carboxylor carboxyalkyl sidechain or a derivative thereof.

In particular, this embodiment of the invention includes:

(3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[N-(3-Bromophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[N-(3-Methylphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[N-(3-Acetylphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[N-(3-Isopropoxyphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[N-(3-Cyanophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-*tert*-butyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-benzoyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-(4-chlorobenzyl)-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[(2S)-2-(3-Trifluoromethylphenylcarbamoylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[(2S)-2-(3-Chlorophenylcarbamoylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[(2S)-2-(N-(3-Chlorophenylcarbamoyl)-methylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[(2S)-2-(3,4-Dichlorophenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[(2S)-2-(2-Methylphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[(2S)-2-(4-Methylphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[(2S)-2-(3-Methoxyphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[(2S)-2-(3-Chlorophenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[N-(3-Chlorophenylcarbamoyl)-valyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[N-(3-Bromophenylcarbamoyl)-valyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[N-(3-Methylphenylcarbamoyl)-isoleucyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[(2S)-2-(3-Chlorophenylcarbamoylamino)-3,3-dimethylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[(S)-α-(3-Chlorophenylcarbamoylamino)-phenylacetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[(S)-α-(3-Methylphenylcarbamoylamino)-cyclohexaneacetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[(2S)-3-(2-Adamantyloxycarbonylamino)-2-(phenylcarbamoylamino)-propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[(2S,3R)-2-(3-Chlorophenylcarbamoylamino)-3-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-[N-(3-Bromophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

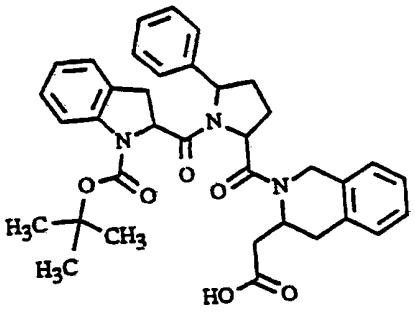
(2R,4S)-1-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-4-phenylpyrrolidine-2-carboxylic acid

(2R,4R)-1-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-4-phenylpyrrolidine-2-acetic acid

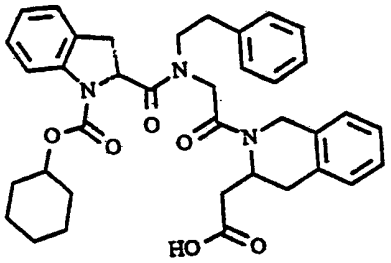
(2R,5S)-1-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-5-phenylpyrrolidine-2-carboxylic acid

(3R)-2-[(2S,3R)-3-Benzyloxy-2-(3-chlorophenylcarbamoylamino)-butyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

The modification of the above structural types to give compounds with consistently high affinity and selectivity for CCK-B/gastrin receptors was more involved, but could be achieved in two ways. The first originated in the discovery that by constraining the conformational freedom of the A subunit with the introduction of L^1 the selectivity for CCK-B receptors was improved. This gain could be further improved by the introduction of L^4 to constrain the B subunit (as in compound f). The affinity and selectivity of these compounds was found to be maintained when L^3 was removed (as in compound g).



f



g

This leads to a fourth preferred embodiment of the present invention, defined precisely in Claims 12-15, in which:

A is a benzo-fused nitrogen heterocyclic acyl residue in which the nitrogen is substituted with a hydrophobic group (i.e. S^1, S^2, L^1 and L^2 all present);

B is a hydrophobic amino-acid residue or a similar surrogate, which preferably incorporates some degree of conformational restriction either through cyclization (as in f or by having a 3-amino-2-naphthoyl residue for B) or through N-substitution (as in g);

C is a benzo-fused piperidine or pyrrolidine which may optionally be substituted at up to three positions. If such substituents are present then at least one is hydrophilic (for example a carboxyl or carboxyalkyl).

In particular, this embodiment of the invention includes:

(3R)-2-{N-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-O-benzyl-threonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{(2S)-2-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonylamino)-4-phenylbutanoyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(2R)-1-{(2S)-2-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetic acid

(3R)-2-{((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-valyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{((2R)-1-*tert*-Butylacetyl-2,3-dihydroindole-2-carbonyl)-valyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-valyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-isoleucyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{(S)-α-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonylamino)-phenylacetyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-D-prolyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{(2R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-2,3-dihydroindole-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{(2R,3S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-3-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{(2R,4S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenylthio-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,4S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenylthio-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{(2R,4R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenylthio-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,4R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-benzyloxy-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,4R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenoxy-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,4R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{(2R,4S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{(2R,4S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-benzyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline

Methyl (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate

(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide

N-{(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carbonyl}-glycine

(3R)-2-{(2R,5S)-1-((2R)-1-Neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,5S)-1-((2R)-1-Isopropyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,5S)-1-((2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,5S)-1-((2R)-1-(2-Adamantyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butylcarbamoyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butylacetyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

N-{(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetyl}-proline

N-{(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetyl}-D-proline

(3R)-2-{(2R,5S)-1-((2R)-1-Neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{(2R,5S)-1-((2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{(2R,5S)-1-((2R)-1-(2-Adamantyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-carboxylic acid

(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-acetic acid

(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-benzyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(2-naphthyl)-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{N-3-Phenylpropyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{N-Benzyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{N-3-Phenylpropyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

(3R)-2-{3-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-amino}-propanoyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{N-Phenethyl-N-((2R)-1-benzyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{N-Phenethyl-N-((2R)-1-neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{N-Phenethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{N-3-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{N-(2-Oxo-2-phenylethyl)-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{N-(2-(3-Indolyl)ethyl)-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-carboxylic acid

(3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-acetic acid
(3R)-2-{N-Pivaloyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-methyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
(3R)-2-{3-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonylamino)-naphthalene-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
(3R)-2-{3-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonylamino)-naphthalene-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
(3R)-2-{(2R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenyl-2,5-dihydropyrrole-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-methyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
(3R)-2-{(2S)-2-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-acetylamino)-4-phenylbutanoyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
N-{(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carbonyl}-proline
N-{(3R)-2-{(2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carbonyl}-proline
N-{(3R)-2-{(2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carbonyl}-D-proline
(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-benzyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
(3R)-2-{N-2-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
(3R)-2-{N-4-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
(3R)-2-{N-2-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
(3R)-2-{N-3-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
(3R)-2-{N-4-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid
(3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[h]isoquinoline-3-carboxylic acid
(4RS)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-4-acetic acid

(4RS)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-4-acetic acid

(3R)-2-{(2R,5S)-1-((2R)-1-Cyclobutyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,5S)-1-((2R)-1-Cyclopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{(2R,5S)-1-((2R)-1-Cyclopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,5S)-1-((2R)-1-(2-*exo*-Norbornyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,5S)-1-((2R)-1-Cyclododecyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{N-Phenethyl-N-((2R)-1-*n*-propyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

N-{(3R)-2-{(2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetyl}-proline

(3R)-2-{N-2-(2-Methoxyphenyl)ethyl-N-((2R)-1-(*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,5S)-1-((2R)-1-(3,3-Dimethylbutyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,5S)-1-((2R)-1-Cycloheptyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,5S)-1-((2R)-1-((1S)-*endo*-Bornyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,5S)-1-((2R)-1-((1R,2R,3R,5S)-Isopinocampheyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,5S)-1-((2R)-1-((1S,2S,3S,5R)-Isopinocampheyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,5S)-1-((2R)-1-(3,3-Dimethylbutyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{(2R,5S)-1-((2R)-1-(1-Piperidino)carbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,5S)-1-((2R)-1-(N-Cyclohexyl-N-methylcarbamoyl)-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,5S)-1-((2R)-1-(4-*tert*-Butylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,5S)-1-((2R)-1-(2-*cis*-Methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,5S)-1-((2R)-1-(2-*trans*-Methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{N-Phenethyl-N-((2R)-1-(3-cyclohexylpropyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{(2R,5S)-1-((2R)-1-Cyclohexylmethyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{(2R,5S)-1-((2R)-1-(2-Cyclohexylethyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

N-{(3R)-2-{(2R,5S)-1-((2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carbonyl}-proline

N-{(3R)-2-{(2R,5S)-1-((2R)-1-Neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carbonyl}-proline

(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-propanoic acid

(3R)-2-{N-3-Methylphenethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{N-(2-(1-Methylpyrrol-2-yl)ethyl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

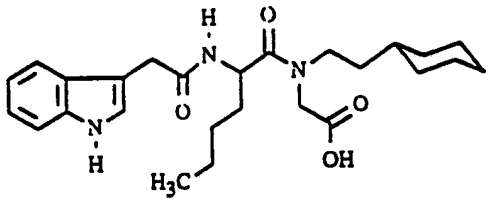
(3R)-2-{N-(2-Thienyl)ethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{N-((2RS)-1,2,3,4-Tetrahydronaphth-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid

(3R)-2-{(2R,5S)-1-((2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(4-methoxyphenyl)-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

(3R)-2-{N-(Indan-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

The second modification which yields potent and selective CCK-B/gastrin receptor ligands involves the deletion of L^5 (equivalent to the excision of the cyclic amide bond from **b**) to give a series of tertiary amides. In this series S^1 is not required and the compounds are structurally less complex (as in **h**).



h

This leads to a fifth preferred embodiment of the present invention, defined precisely in Claims 8-11, in which:

A is an acyl residue with an aromatic substituent;

B is a hydrophobic amino-acid or a similar surrogate;

C is an N-substituted amino-acid or similar surrogate, where the N-substituent is an alkyl, cycloalkyl, aralkyl or aryl group, and the carboxy terminus may be the free acid or may be blocked as an ester or amide, or may be extended, for example, by acylating another amino-acid residue.

In particular, this preferred embodiment of the invention includes:

Methyl N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycinate

N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycine

1-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-pyrrolidine

Methyl N-{N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-prolinate

N-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-proline

N-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-pipecolic acid

N-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-glycine

1-{N-(2-Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-pyrrolidine

1-{N-(2-Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-proline

1-{N-(2-Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-proline
1-{N-(Cyclooctylmethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-proline
1-{3-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-amino}-propanoyl}-pyrrolidine
N-(3-Cyclohexylpropyl)-N-((2S)-2-(2-indolecarbonylamino)-hexanoyl)-glycine
N-(3-Cyclohexylpropyl)-N-(N-(3-indoleacetyl)-phenylalanyl)-glycine
N-(2-Cyclohexylethyl)-N-((2S)-2-(3-isoquinolinecarbonylamino)-4-phenylbutanoyl)-glycine
N-{N-Phenethyl-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-proline.
1-{N-(2-Cyclohexylethyl)-N-(N-(3-indoleacetyl)-phenylalanyl)-glycyl}-D-proline
1-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-4-phenylbutanoyl)-glycyl}-D-proline

Where the compounds of the present invention are capable of forming salts with inorganic and organic acids and/or bases then those pharmaceutically acceptable salts are included within the scope of the invention. Examples of such salts include sodium, potassium and tetra-alkyl ammonium salts of acidic compounds, and chlorides, sulphates and acetates of basic compounds.

Where the compounds of the present invention contain a carboxylic acid moiety then these may be administered in pro-drug form as simple esters.

SYNTHETIC METHODS

GENERAL

The synthesis of the compounds of the present invention can be considered as involving two stages. In Stage 1 the individual components **A**, **B** and **C** in general formula **I** are prepared from commercially available starting materials if they are not themselves available. During Stage 1 protecting groups may be introduced into **A**, **B** and **C** in order to obviate side reactions in Stage 2. The second phase involves assembling the individual components into the finished compound. During Stage 2, apart from the crucial **A**-**B** and **B**-**C** bond forming reactions, selective manipulation of the protecting groups may be necessary. At the end of Stage 2 final adjustments can be made to complete the synthesis.

Using general formula **I** as the target, a typical synthesis might involve the following steps:

Stage 1

pre-A ⇨ steps ⇨ PG^1-A

pre-B ⇨ steps ⇨ PG^2-B

pre-C ⇨ steps ⇨ C-PG^3

where PG^1 - PG^3 are protecting groups,

pre-A - *pre*-C are commercially available precursors.

Stage 2

PG^2-B + C-PG^3 ⇨ PG^2-B-C-PG^3

PG^2-B-C-PG^3 ⇨ B-C-PG^3

PG^1-A + B-C-PG^3 ⇨ PG^1-A-B-C-PG^3

PG^1-A-B-C-PG^3 ⇨ A-B-C

Depending on the precise nature of A, B and C the order in which the components are coupled together may be varied. Thus it might be advantageous to form the A-B fragment first and couple this to C. Another variation is possible when C can be divided into two sub-fragments (e.g. when C is **XIX**, or **XVI** with R^{14} is **XXII**). In these cases one of the sub-fragments can be introduced at a late stage. If C is composed of the sub-fragments C^1-D then Stage 2 of the overall synthesis might be:

PG^2-B + C^1-PG^3 ⇨ PG^2-B-C^1-PG^3

PG^2-B-C^1-PG^3 ⇨ B-C^1-PG^3

PG^1-A + B-C^1-PG^3 ⇨ PG^1-A-B-C^1-PG^3

PG^1-A-B-C^1-PG^3 ⇨ PG^1-A-B-C^1

PG^1-A-B-C^1 + D ⇨ PG^1-A-B-C

PG^1-A-B-C ⇨ A-B-C

The chemistry involved in preparing the compounds of the present invention depends on the nature of A, B and C. The specific Examples which follow make use of reactions which are established in the literature for analogous transformations. It is not the inventors' intention to restrict the scope of this patent solely to those reactions described explicitly in the Examples, but to include other methods which a person competent in the art might employ to achieve the same overall transformation. Also included are such

variations in the protecting groups and the order of assembly of the fragments as might be used by such a competent person.

The general concepts outlined above (preparation of the fragments, coupling, and protecting group manipulation) will now be illustrated more fully in the following non-limiting Examples.

EXPLANATORY NOTES

In the following Examples:

R_f: TLC was performed on commercial silica plates (Merck Art. 5714)

HPLC: Buffer I 0.1% TFA/H_2O; Buffer II 0.1% TFA/MeCN

System A: Novapak C_{18}, 4 μ, 8x100 mm; linear gradient 40% to 90% II into I over 25 min. at 1.5 mL/min.

System B: Spherisorb C_{18}, 5 μ, 4.6x100 mm; linear gradient 40% to 90% II into I over 25 min. at 0.8 mL/min.

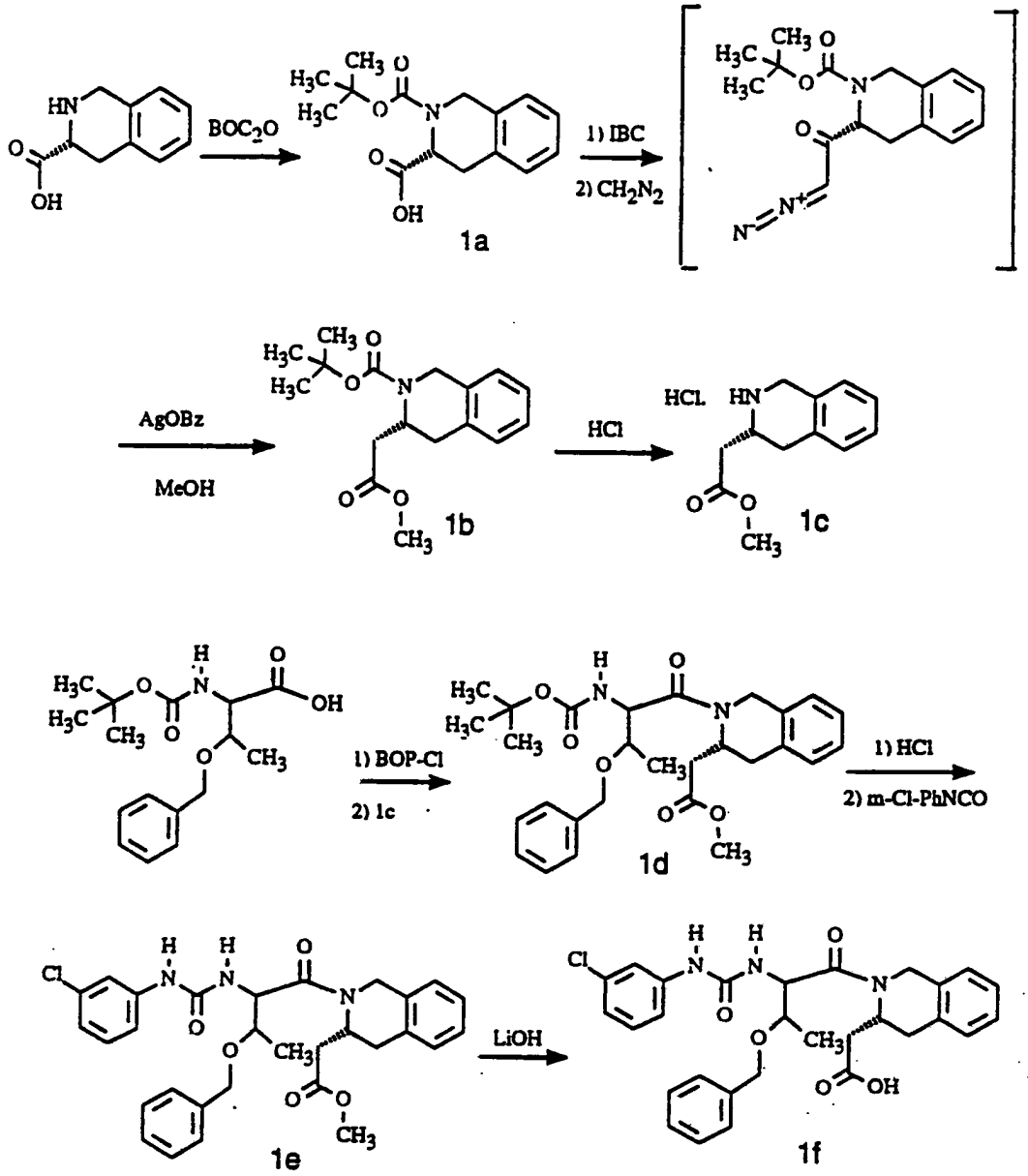
AAA: Hydrolysis 6*N* HCl + phenol at 150°C for 1.5 hr.

^1H NMR: Determined at 270 MHz in $CDCl_3$.

Mass spec: Positive ion FAB.

Reagents were generally used as supplied without purification. Solvents were HPLC grade, except THF which was distilled from Na/benzophenone. Silica gel for flash chromatography was Merck Kieselgel 60 (230-400 mesh).

EXAMPLE 1



1a (3R)-2-*tert*-Butyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

To a stirred suspension of D-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (2.5 g, 14.1 mmol) in dioxan (200 mL) was added di-*tert*-butyl pyrocarbonate (3.66 g, 16.9 mmol) and a solution of KOH (0.79 g, 14.1 mmol) in H_2O (50 mL). The mixture was stirred at room temperature for 5 hr., and then the solvent was evaporated *in vacuo*. The residue was taken up in H_2O and the solution was acidified with 10% aq. $KHSO_4$ to pH=2. The mixture was extracted twice with EtOAc, and the combined extracts were

washed with brine, filtered (Whatman® 1 PS phase separator), and concentrated *in vacuo*. The residue was triturated with pet. ether (b.p. 60-80°C) to give the title compound as a white solid (3.2 g, 82%).

1b Methyl (3R)-2-*tert*-Butyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-acetate.

To a stirred solution of **1a** (10.9 g, 39.5 mmol) in EtOAc (120 mL) was added N-methylmorpholine (4.4 mL, 40 mmol). The solution was cooled to -20°C, and isobutyl chloroformate (5.2 mL, 44 mmol) was added dropwise. The mixture was stirred at -15°C for 20 min., then poured into a solution of diazomethane (from Diazald®, 43 g, 200 mmol) in Et_2O, and the resulting solution was stirred at room temperature for 1 hr. Excess diazomethane was destroyed by the addition of glacial AcOH. The solution was washed successively with 1.0*M* $NaHCO_3$, H_2O and brine, dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:pet ether 25:75 v/v) to give (3R)-2-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydroisoquinolyl diazomethyl ketone (8.0 g, 26.6 mmol, 67%).

This ketone was dissolved in MeOH (200 mL) and to this solution was added a solution of silver benzoate (2 g, 8 mmol) in Et_3N. The mixture was stirred at room temperature for 40 min., and then the solvent was evaporated *in vacuo*. The residue was taken up in EtOAc and washed successively with 1.0*M* $NaHCO_3$, H_2O, brine, 0.3*M* $KHSO_4$, H_2O and brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:pet. ether 18:82 v/v) to give the title ester (6.5 g, 80%).

1c Methyl (3R)-1,2,3,4-tetrahydroisoquinoline-3-acetate hydrochloride.

The BOC-protected ester **1b** (6.5 g, 21.3 mmol) was taken up in 4*N* HCl in dioxan (100 mL) and the solution was stirred at room temperature for 90 min. The solvent was removed *in vacuo*, finally with toluene azeotrope, to give the title compound (5.0 g, 99%).

1d Methyl (3R)-2-[N-*tert*-butyloxycarbonyl-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

To a stirred solution of BOC-(O-benzyl)-threonine (866 mg, 2.8 mmol) and diisopropylethylamine (0.50 mL, 2.88 mmol) in CH_2Cl_2 (20 mL), cooled to -20°C, was added *bis*(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl, 733 mg, 2.88 mmol). The mixture was stirred at -20°C for 20 min., then **1c** (483 mg, 2 mmol) and diisopropylethylamine (0.35 mL, 2 mmol) were added. The mixture was stirred at room temperature overnight, then poured into EtOAC. The solution was washed successively

with 10% $KHSO_4$, satd. $KHCO_3$, H_2O and brine, filtered (Whatman^R 1PS phase separator), and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:hexane 25:75 v/v) to give the title compound (678 mg, 68%).

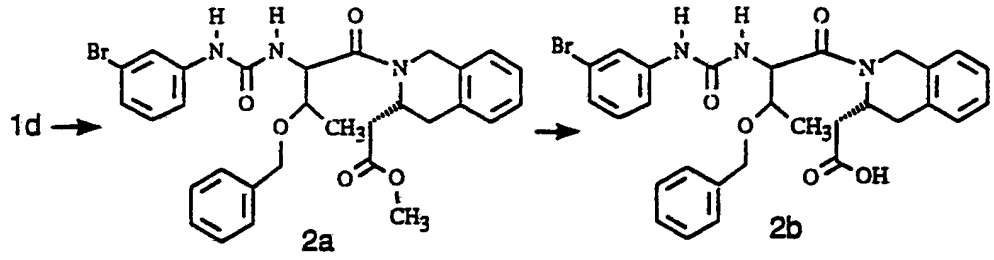
1e Methyl (3R)-2-[N-(3-chlorophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

A solution of the BOC-protected ester **1d** (159 mg, 0.32 mmol) in 4*N* HCl in dioxan (10 mL) was stirred at room temperature for 90 min., then the solvent was removed *in vacuo*, finally with toluene azeotrope. The residue was taken up in CH_2Cl_2 (10mL) and cooled to 0°C. Diisopropylethylamine (60 µL, 0.32 mmol) was added, then 3-chlorophenylisocyanate (43 µL, 0.35 mmol), and the mixture was stirred at 0°C for 2 hr. The mixture was then diluted with EtOAc and washed successively with 10% $KHSO_4$, satd. $KHCO_3$, H_2O and brine, filtered (Whatman^R 1PS phase separator) and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v) to give the title compound (152 mg, 86%).
R_f (EtOAc:hexane 50:50 v/v) 0.31

1f (3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

To a stirred solution of the ester **1e** (152 mg, 0.27 mmol) in dioxan (10mL) was added a solution of LiOH (13 mg, 0.54 mmol) in H_2O (5mL). The mixture was stirred at room temperature for 1 hr., then the solvent was removed *in vacuo*. The residue was partitioned between EtOAc and aq. $KHSO_4$. The organic phase was washed with brine, filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 65:35:1 v/v/v), and the product was taken up in acetonitrile/water and lyophilised to give the title compound (95 mg, 66%).
R_f (EtOAc:hexane:AcOH 70:30:1 v/v/v) 0.20
HPLC System A t_R=15.9' >99%
Mass spec (FAB) m/e=536 $[M+H]^+$

EXAMPLE 2



2a Methyl (3R)-2-[N-(3-bromophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1e** on a 0.32 mmol scale using **1d** and 3-bromophenylisocyanate. The product was isolated in 71% yield after flash chromatography on silica gel (eluant EtOAc:hexane 50:50 v/v).

R_f (EtOAc:hexane 50:50 v/v) 0.30

2b (3R)-2-[N-(3-Bromophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

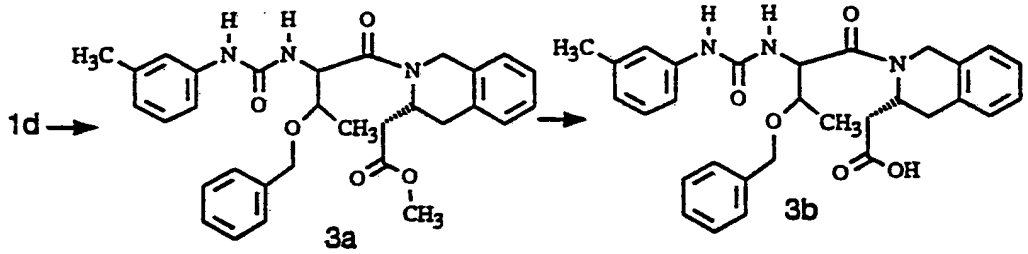
This was prepared from **2a** on a 0.23 mmol scale following the method described for **1f.** The product was isolated in 59% yield (79 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 65:35:1 v/v/v).

R_f (EtOAc:hexane:AcOH 70:30:1 v/v/v) 0.20

HPLC System A t_R=16.1' >98%

Mass spec (FAB) m/e=582 $[M+H]^+$

EXAMPLE 3



3a Methyl (3R)-2-[N-(3-methylphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1e** on a 0.68 mmol scale using **1d** and 3-methylphenylisocyanate. The product was isolated in 67% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

R_f (EtOAc:hexane:AcOH 50:50:1 v/v/v) 0.37

3b (3R)-2-[N-(3-Methylphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

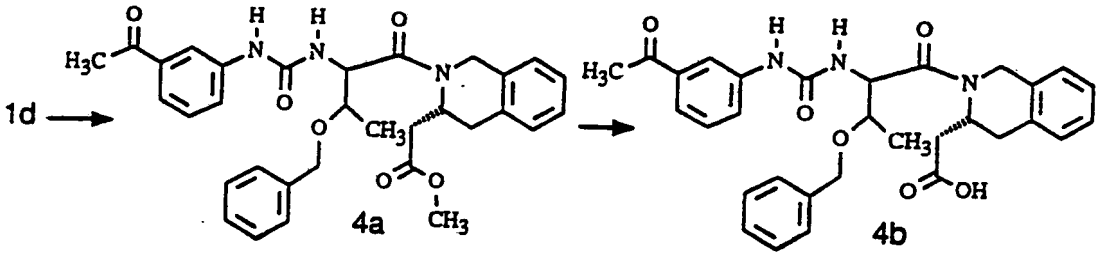
This was prepared from **3a** on a 0.46 mmol scale following the method described for **1f**. The product was isolated in 68% yield (162 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 50:50:1 v/v/v).

R_f (EtOAc:hexane:AcOH 50:50:1 v/v/v) 0.20

HPLC System A t_R=14.7' >99%

Mass spec (FAB) m/e=516 $[M+H]^+$

EXAMPLE 4



4a Methyl (3R)-2-[N-(3-acetylphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1e** on a 0.21 mmol scale using **1d** and 3-acetylphenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 45:55 v/v).

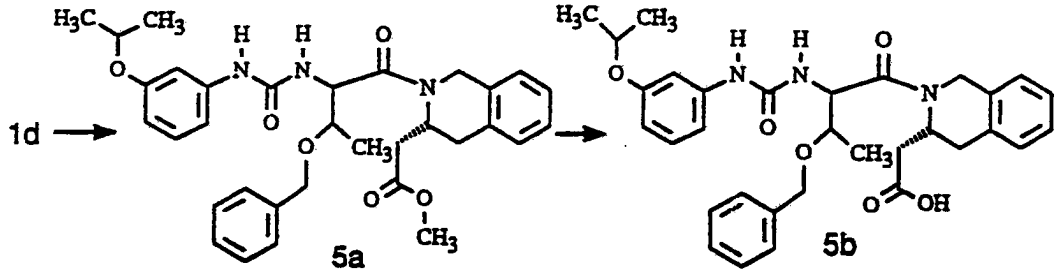
4b (3R)-2-[N-(3-Acetylphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **4b** on a 0.21 mmol scale following the method described for **1f**. The product was isolated in 53% yield (61 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).

HPLC System B t_R=8.8' >95%

Mass spec (FAB) m/e=544 $[M+H]^+$

EXAMPLE 5



5a Methyl (3R)-2-[N-(3-isopropoxyphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1e** on a 0.31 mmol scale using **1d** and 3-isopropoxyphenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

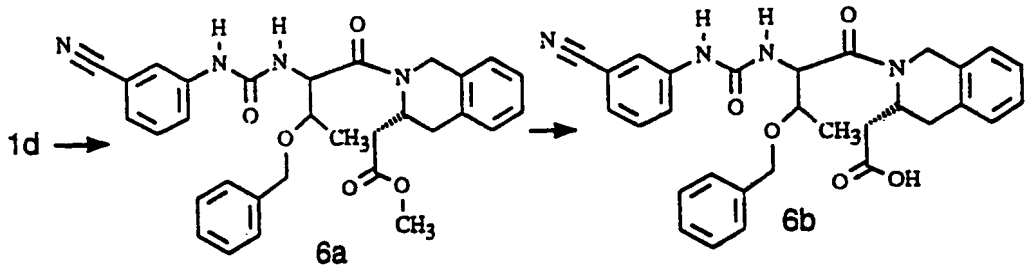
5b (3R)-2-[N-(3-Isopropoxyphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **5a** on a 0.31 mmol scale following the method described for **1f**. The product was isolated in 40% yield (69 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 45:55:2 v/v/v).

HPLC System B t_R=12.5' >95%

Mass spec (FAB) m/e=560 $[M+H]^+$

EXAMPLE 6



6a Methyl (3R)-2-[N-(3-cyanophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1e** on a 0.31 mmol scale using **1d** and 3-cyanophenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

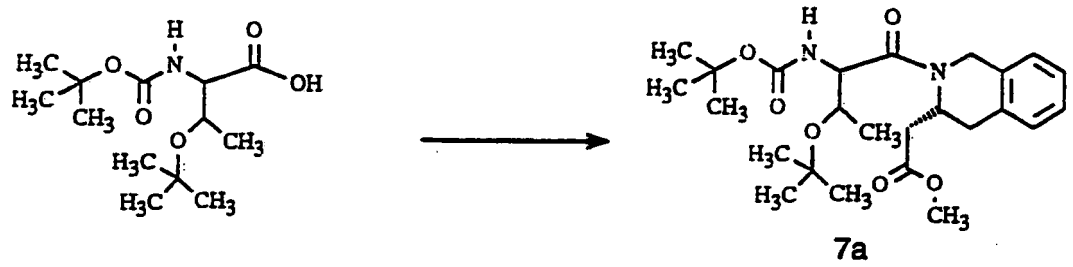
6b (3R)-2-[N-(3-Cyanophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **6a** on a 0.31 mmol scale following the method described for **1f**. The product was isolated in 34% yield (55 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

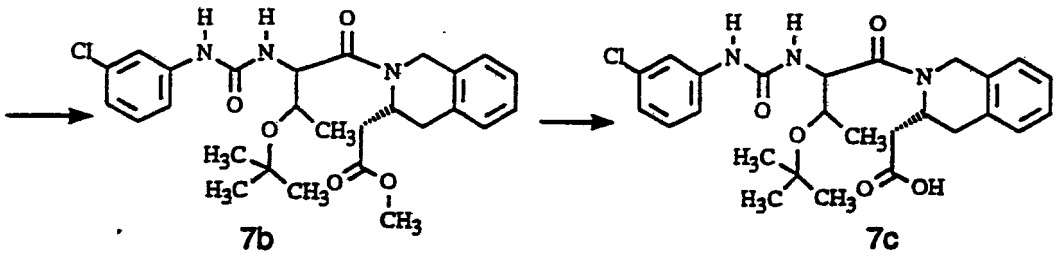
HPLC System A t_R=13.3' 80%

Mass spec (FAB) m/e=527 $[M+H]^+$

EXAMPLE 7



7a



7b 7c

7a Methyl (3R)-2-[N-*tert*-butyloxycarbonyl-O-*tert*-butyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1d** on a 0.41 mmol scale using N-BOC-O-*tert*-butyl-threonine instead of N-BOC-O-benzyl-threonine. The product was isolated in 74% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

7b Methyl (3R)-2-[N-(3-chlorophenylcarbamoyl)-O-*tert*-butyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1e** on a 0.30 mmol scale using **7a** and 3-chlorophenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

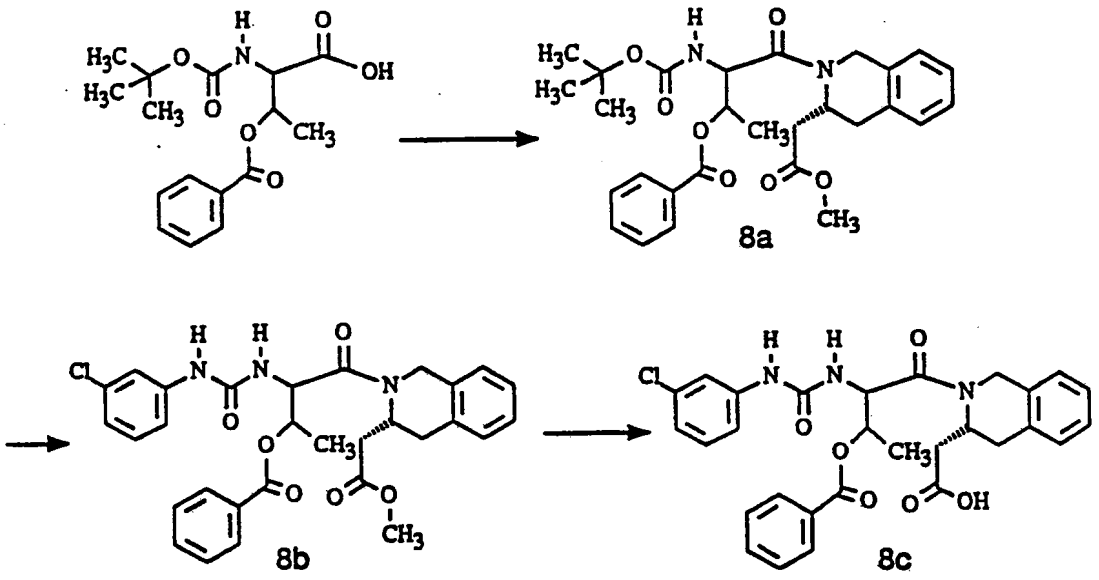
7c (3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-*tert*-butyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **7b** on a 0.30 mmol scale following the method described for **1f**. The product was isolated in 56% yield (84 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

HPLC System A t_R=15.2' >95%

Mass spec (FAB) m/e=502 $[M+H]^+$

EXAMPLE 8



8a Methyl (3R)-2-[N-*tert*-butyloxycarbonyl-O-benzoyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1d** on a 0.50 mmol scale using N-BOC-O-benzoyl-threonine instead of N-BOC-O-benzyl-threonine. The product was isolated in 55% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

8b Methyl (3R)-2-[N-(3-chlorophenylcarbamoyl)-O-benzoyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1e** on a 0.27 mmol scale using **8a** and 3-chlorophenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

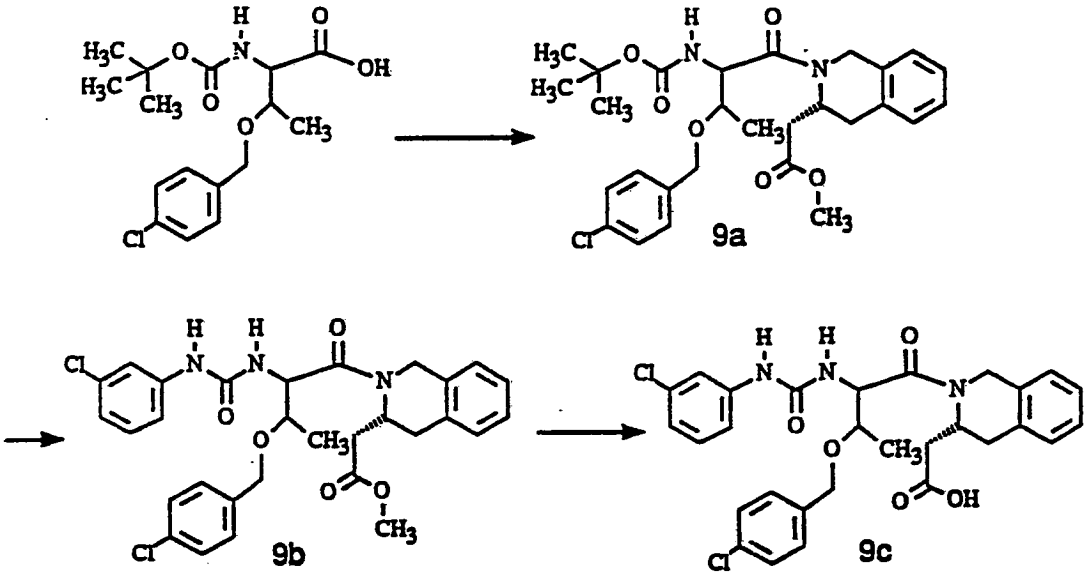
8c (3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-benzoyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **8b** on a 0.27 mmol scale following the method described for **1f**. The product was isolated in 35% yield (52 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 45:55:2 v/v/v).

HPLC System B t_R=12.2' >95%

Mass spec (FAB) m/e=550 $[M+H]^+$

EXAMPLE 9



9a Methyl (3R)-2-[N-*tert*-butyloxycarbonyl-O-(4-chlorobenzyl)-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1d** on a 0.50 mmol scale using N-BOC-O-(4-chlorobenzyl)-threonine instead of N-BOC-O-benzyl-threonine. The product was isolated in 70% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

9b Methyl (3R)-2-[N-(3-chlorophenylcarbamoyl)-O-(4-chlorobenzyl)-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1e** on a 0.35 mmol scale using **9a** and 3-chlorophenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

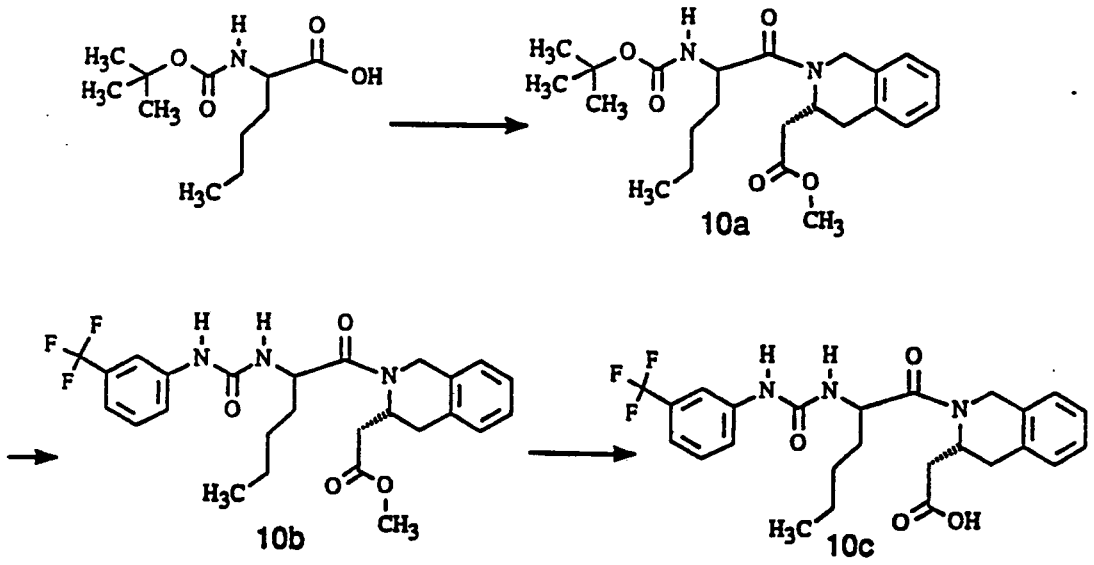
9c (3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-(4-chlorobenzyl)-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **9b** on a 0.35 mmol scale following the method described for **1f**. The product was isolated in 64% yield (127 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

HPLC System A t_R=18.0' >99%

Mass spec (FAB) m/e=570 $[M+H]^+$

EXAMPLE 10



10a Methyl (3R)-2-[(2S)-2-*tert*-butyloxycarbonylaminohexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1d** on a 4.0 mmol scale using N-BOC-(2S)-2-aminohexanoic acid instead of N-BOC-O-benzyl-threonine. The product was isolated in 66% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

10b Methyl (3R)-2-[(2S)-2-(3-trifluoromethylphenylcarbamoylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1e** on a 0.32 mmol scale using **10a** and 3-trifluoromethylphenylisocyanate. The product was isolated in 52% after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 30:70:1 v/v/v).

R_f (EtOAc:pet. ether:AcOH 30:70:1 v/v/v) 0.31

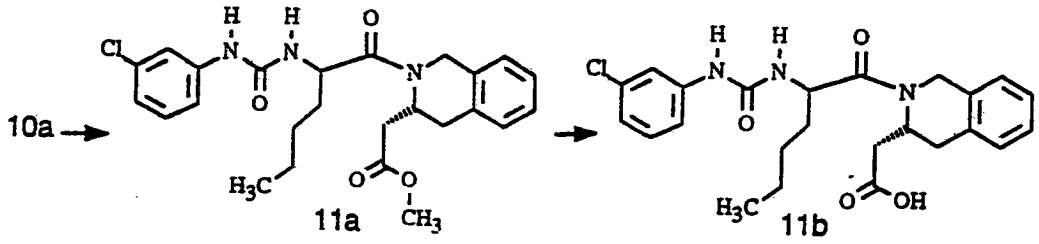
^1H NMR δ 0.90 (3H,2t); 1.2-1.8 (m); 3.6 (3H,2s)

10c (3R)-2-[(2S)-2-(3-Trifluoromethylphenylcarbamoylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **10b** on a 0.16 mmol scale following the method described for **1f**. The product was isolated in 70% yield (55 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).

HPLC System B t_R=12.2' >98%
Mass spec (FAB) m/e=492 $[M+H]^+$

EXAMPLE 11



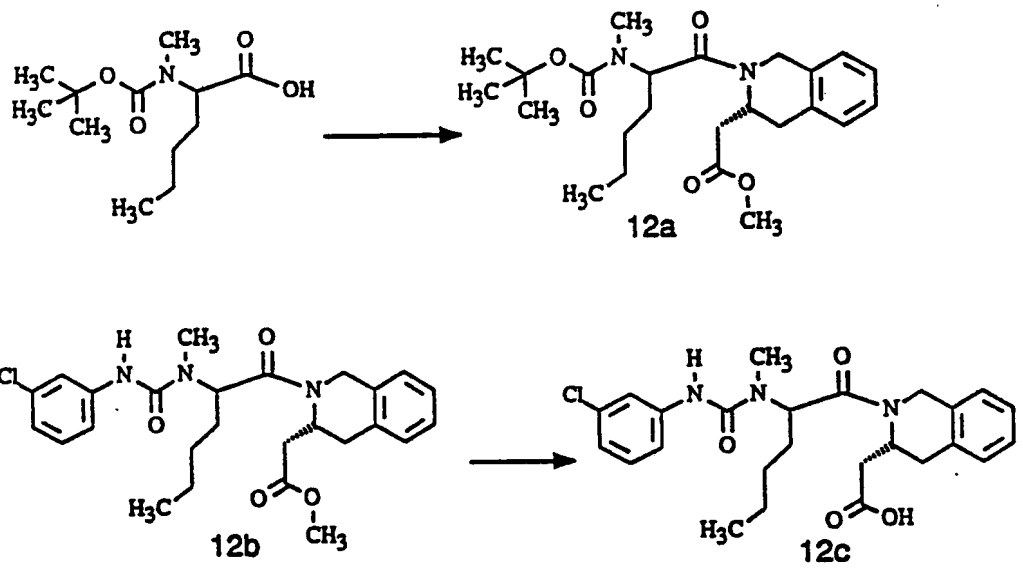
11a Methyl (3R)-2-[(2S)-2-(3-chlorophenylcarbamoylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1e** on a 0.26 mmol scale using **10a** and 3-chlorophenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

11b (3R)-2-[(2S)-2-(3-Chlorophenylcarbamoylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **11a** on a 0.26 mmol scale following the method described for **1f**. The product was isolated in 61% yield (73 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).
HPLC System A t_R=14.1' >98%
Mass spec (FAB) m/e=458 $[M+H]^+$

EXAMPLE 12



12a Methyl (3R)-2-[(2S)-2-(N-*tert*-butyloxycarbonyl)methylaminohexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1d** on a 0.40 mmol scale using N-BOC-(2S)-2-methylaminohexanoic acid instead of N-BOC-O-benzyl-threonine. The product was isolated in 57% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).

12b Methyl (3R)-2-[(2S)-2-(N-(3-chlorophenylcarbamoyl)-methylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1e** on a 0.23 mmol scale using **12a** and 3-chlorophenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

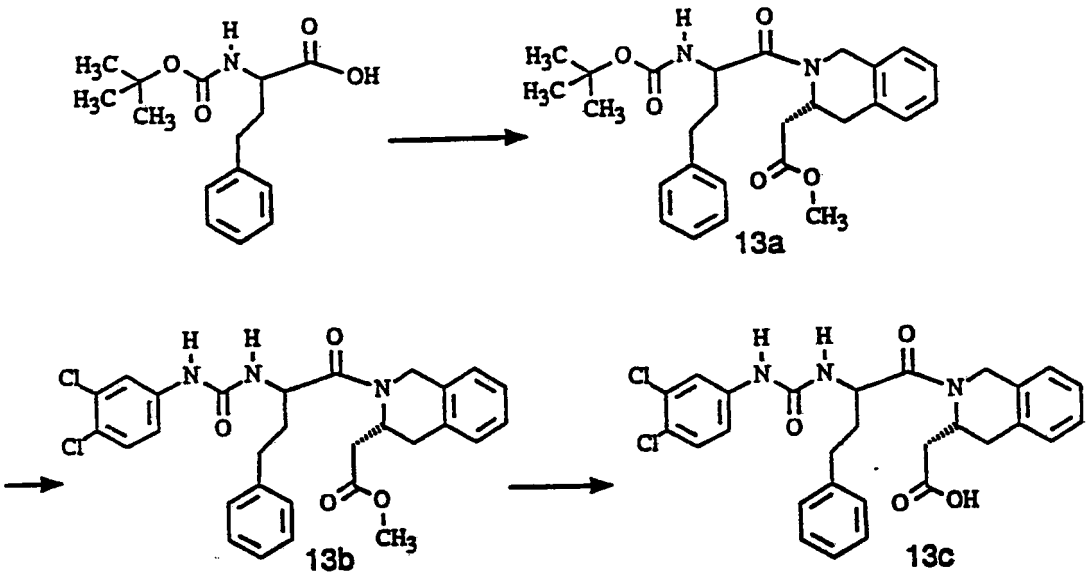
12c (3R)-2-[(2S)-2-(N-(3-Chlorophenylcarbamoyl)-methylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **12b** on a 0.23 mmol scale following the method described for **1f**. The product was isolated in 44% yield (48 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

HPLC System A t_R=14.8' >98%

Mass spec (FAB) m/e=472 $[M+H]^+$

EXAMPLE 13



13a Methyl (3R)-2-[(2S)-2-*tert*-butyloxycarbonylamino-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1d** on a 1.27 mmol scale using N-BOC-(2S)-2-amino-4-phenylbutanoic acid instead of N-BOC-O-benzyl-threonine. The product was isolated in 71% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 60:40 v/v).

R_f (EtOAc:pet. ether 30:70 v/v) 0.19

13b Methyl (3R)-2-[(2S)-2-(3,4-dichlorophenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1e** on a 0.30 mmol scale using **13a** and 3,4-dichlorophenylisocyanate. The product was isolated in 49% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 30:70:1 v/v/v).

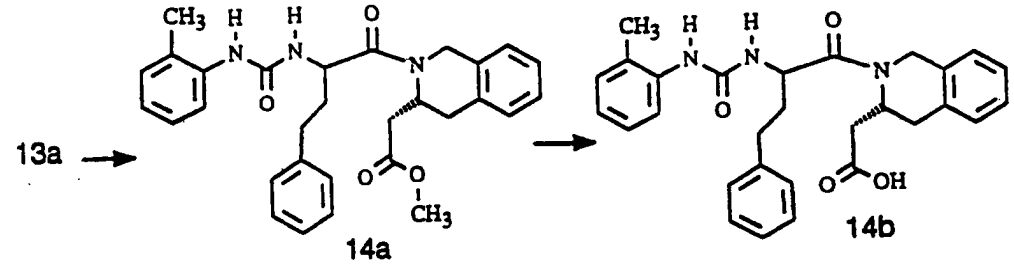
^{1}H NMR δ 3.74,3.64,3.61 (3H,3s)

13c (3R)-2-[(2S)-2-(3,4-Dichlorophenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **13b** on a 0.15 mmol scale following the method described for **1f**. The product was isolated in 76% yield (62 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 70:30:1 v/v/v).

HPLC System B t_R=14.4' 80%
Mass spec (FAB) m/e=540 $[M+H]^+$

EXAMPLE 14



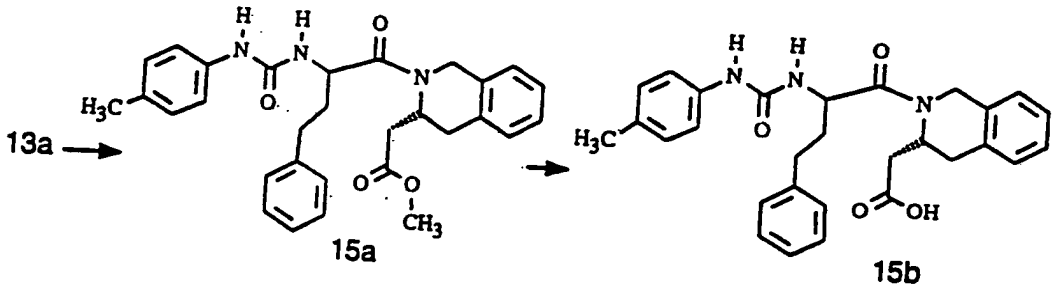
14a Methyl (3R)-2-[(2S)-2-(2-methylphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1e** on a 0.33 mmol scale using **13a** and 2-methylphenylisocyanate. The product was isolated in 85% yield and used without purification.

14b (3R)-2-[(2S)-2-(2-Methylphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **14a** on a 0.28 mmol scale following the method described for **1f**. The product was isolated in 58% yield (78 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:1 v/v/v).
HPLC System B t_R=10.3' >98%
Mass spec (FAB) m/e=486 $[M+H]^+$

EXAMPLE 15



15a Methyl (3R)-2-[(2S)-2-(4-methylphenylcarbamoylamino)-4-phenylbutanoyl]-1.2.3.4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1e on a 0.33 mmol scale using 13a and 4-methylphenylisocyanate. The product was isolated in 91% yield and used without purification.

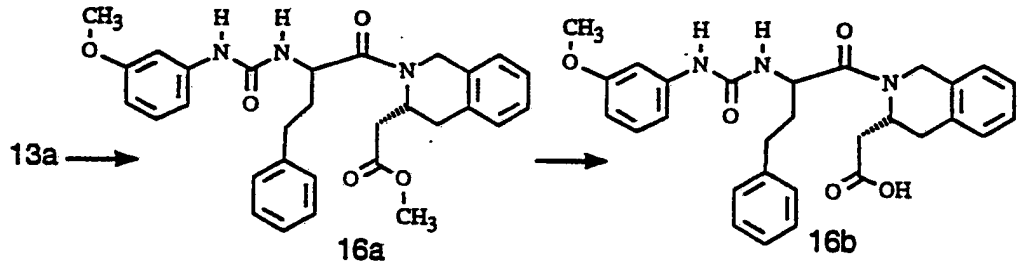
15b (3R)-2-[(2S)-2-(4-Methylphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 15a on a 0.30 mmol scale following the method described for 1f. The product was isolated in 69% yield (101 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:1 v/v/v).

HPLC System B t_R=11.1' >97%

Mass spec (FAB) m/e=486 $[M+H]^+$

EXAMPLE 16



16a Methyl (3R)-2-[(2S)-2-(3-methoxyphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

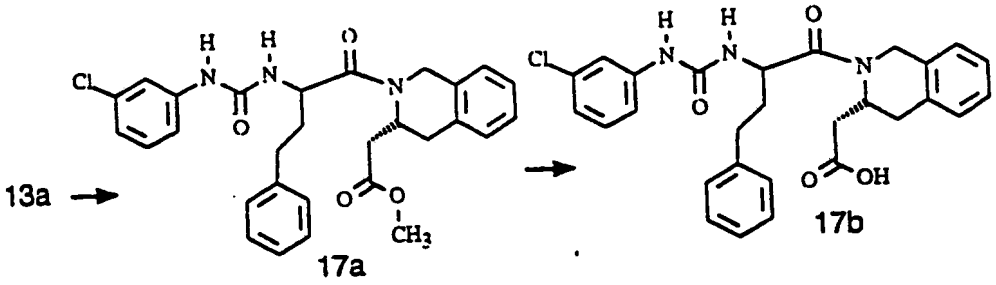
This was prepared following the method described for 1e on a 0.20 mmol scale using 13a and 3-methoxyphenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 45:55 v/v).

16b (3R)-2-[(2S)-2-(3-Methoxyphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 16a on a 0.20 mmol scale following the method described for 1f. The product was isolated in 52% yield (52 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).

HPLC System A t_R=12.9' >99%
Mass spec (FAB) m/e=502 $[M+H]^+$

EXAMPLE 17



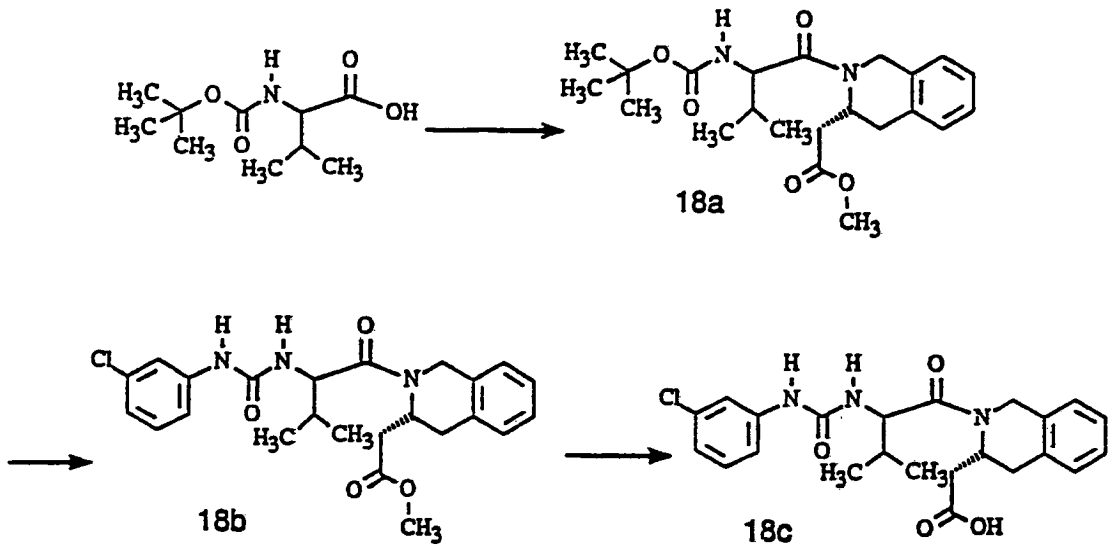
17a Methyl (3R)-2-[(2S)-2-(3-chlorophenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1e** on a 0.20 mmol scale using **13a** and 3-chlorophenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 45:55 v/v).

17b (3R)-2-[(2S)-2-(3-Chlorophenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **17a** on a 0.20 mmol scale following the method described for **1f**. The product was isolated in 74% yield (75 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).
HPLC System A t_R=15.6' >98%
Mass spec (FAB) m/e=506 $[M+H]^+$

EXAMPLE 18



18a Methyl (3R)-2-[N-*tert*-butyloxycarbonyl-valyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1d** on a 3.0 mmol scale using N-BOC-valine instead of N-BOC-O-benzyl-threonine. The product was isolated in 54% yield after flash chromatography on silica gel (eluant EtOAc:hexane 20:80 v/v).

R_f (EtOAc:hexane 20:80 v/v) 0.27

18b Methyl (3R)-2-[N-(3-chlorophenylcarbamoyl)-valyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1e on a 0.47 mmol scale using **18a** and 3-chlorophenylisocyanate. The product was isolated in 61% yield and used without purification.

R_f (EtOAc:hexane 60:40 v/v) 0.33

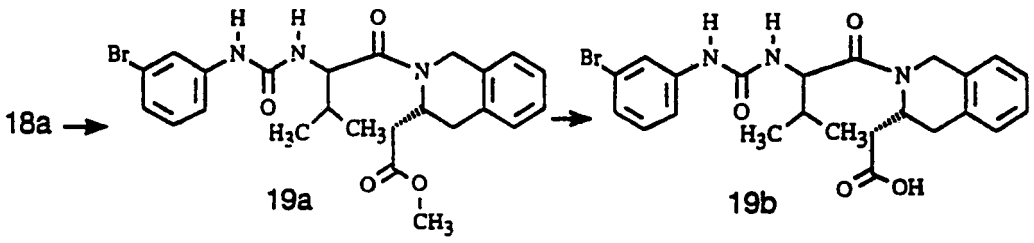
18c (3R)-2-[N-(3-Chlorophenylcarbamoyl)-valyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **18b** on a 0.29 mmol scale following the method described for **1f**. The product was isolated in 47% yield (60 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 60:40:2 v/v/v).

R_f (EtOAc:hexane:AcOH 60:40:1 v/v/v) 0.23

HPLC System A t_R=11.9' >90%
Mass spec (FAB) m/e=444 $[M+H]^+$

EXAMPLE 19



19a Methyl (3R)-2-[N-(3-bromophenylcarbamoyl)-valyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1e** on a 0.47 mmol scale using **18a** and 3-bromophenylisocyanate. The product was isolated in 61% yield and used without purification.

R_f (EtOAc:hexane 60:40 v/v) 0.33

19b (3R)-2-[N-(3-Bromophenylcarbamoyl)-valyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

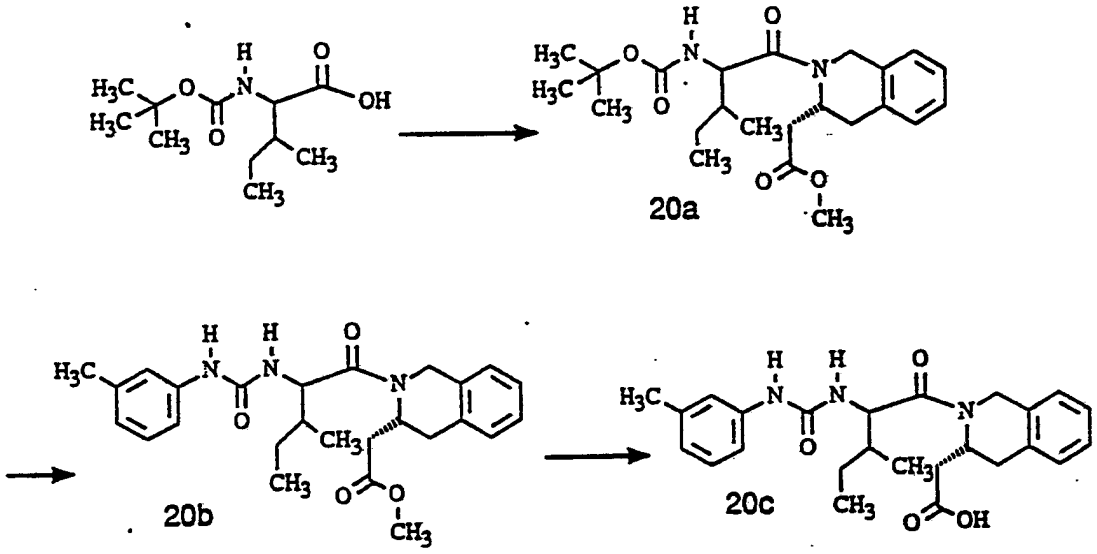
This was prepared from **19a** on a 0.29 mmol scale following the method described for **1f**. The product was isolated in 60% yield (85 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 60:40:2 v/v/v).

R_f (EtOAc:hexane:AcOH 60:40:1 v/v/v) 0.24

HPLC System A t_R=12.5' >98%

Mass spec (FAB) m/e=489 $[M+H]^+$

EXAMPLE 20



20a Methyl (3R)-2-[N-*tert*-butyloxycarbonyl-isoleucyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1d** on a 0.58 mmol scale using N-BOC-isoleucine instead of N-BOC-O-benzyl-threonine. The product was isolated in 56% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

20b Methyl (3R)-2-[N-(3-methylphenylcarbamoyl)-isoleucyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1e** on a 0.16 mmol scale using **20a** and 3-methylphenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

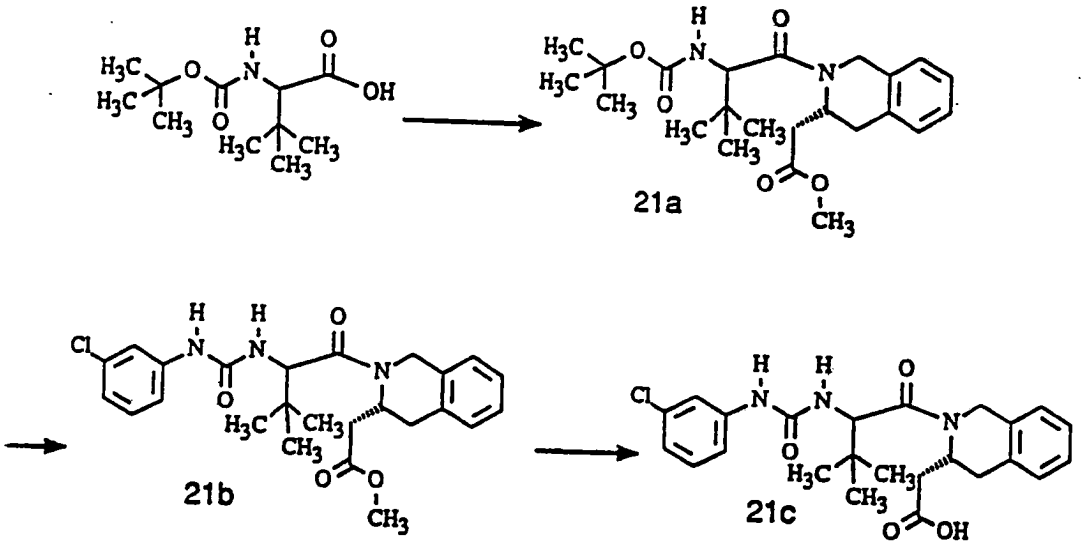
20c (3R)-2-[N-(3-Methylphenylcarbamoyl)-isoleucyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **20b** on a 0.16 mmol scale following the method described for **1f**. The product was isolated in 70% yield (49 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

HPLC System A t_R=12.4' >98%

Mass spec (FAB) m/e=438 $[M+H]^+$

EXAMPLE 21



21a Methyl (3R)-2-[(2S)-2-*tert*-butyloxycarbonylamino-3,3-dimethylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1d** on a 0.75 mmol scale using N-BOC-(2S)-2-amino-3,3-dimethylbutanoic acid instead of N-BOC-O-benzyl-threonine. The product was isolated in 18% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

21b Methyl (3R)-2-[(2S)-2-(3-chlorophenylcarbamoylamino)-3,3-dimethylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1e** on a 0.14 mmol scale using **21a** and 3-chlorophenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

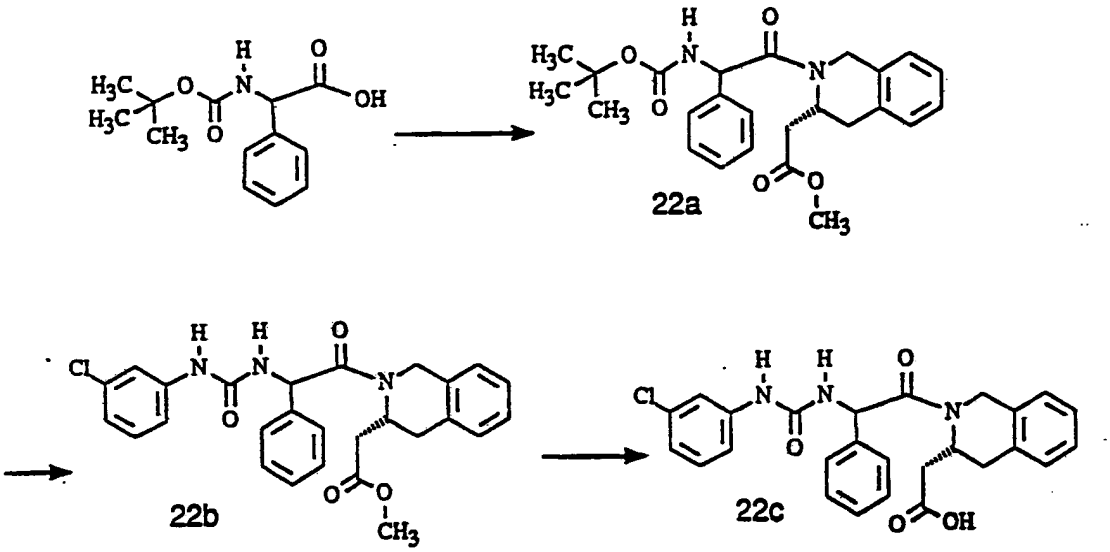
21c (3R)-2-[(2S)-2-(3-Chlorophenylcarbamoylamino)-3,3-dimethylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **21b** on a 0.14 mmol scale following the method described for **1f**. The product was isolated in 73% yield (47 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

HPLC System B t_R=10.6' >99%

Mass spec (FAB) m/e=458 $[M+H]^+$

EXAMPLE 22



22a Methyl (3R)-2-[(S)-α-*tert*-butyloxycarbonylamino-phenylacetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1d** on a 0.50 mmol scale using N-BOC-(S)-α-amino-phenylacetic acid instead of N-BOC-O-benzyl-threonine. The product was isolated in 68% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

22b Methyl (3R)-2-[(S)-α-(3-chlorophenylcarbamoylamino)-phenylacetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1e** on a 0.34 mmol scale using **22a** and 3-chlorophenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

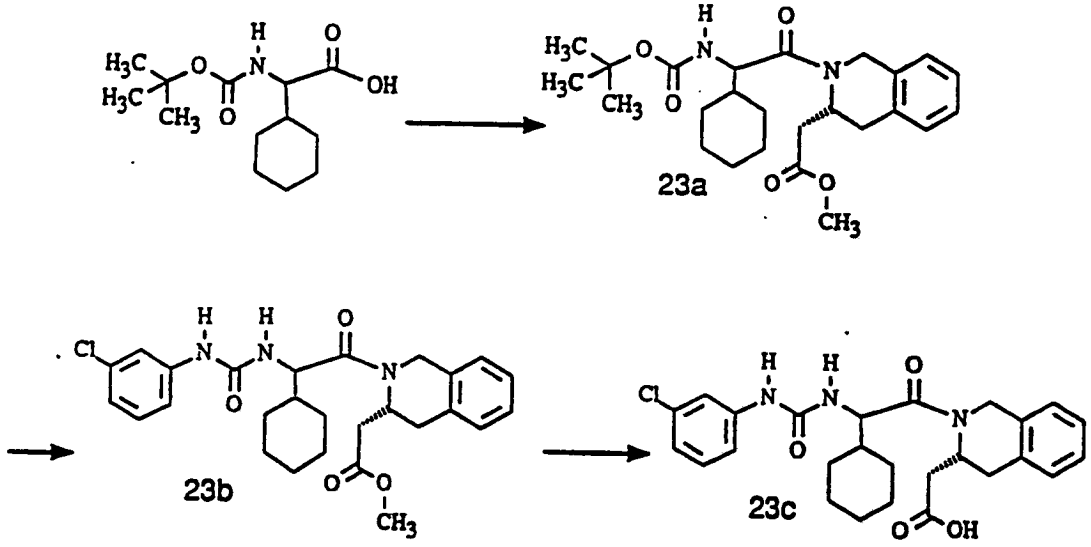
22c (3R)-2-[(S)-α-(3-Chlorophenylcarbamoylamino)-phenylacetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **22b** on a 0.34 mmol scale following the method described for **1f**. The product was isolated in 64% yield (104 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

HPLC System A t_R=13.8' >95%

Mass spec (FAB) m/e=478 $[M+H]^+$

EXAMPLE 23



23a Methyl (3R)-2-[(S)-α-*tert*-butyloxycarbonylamino-cyclohexaneacetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1d** on a 2.0 mmol scale using N-BOC-(S)-α-amino-cyclohexaneacetic acid instead of N-BOC-O-benzyl-threonine. The product was isolated in 58% yield after flash chromatography on silica gel (eluant EtOAc:hexane 25:75 v/v).

R_f (EtOAc:hexane 20:80 v/v) 0.32

23b Methyl (3R)-2-[(S)-α-(3-methylphenylcarbamoylamino)-cyclohexaneacetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1e** on a 0.58 mmol scale using **23a** and 3-methylphenylisocyanate. The product was isolated in 76% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

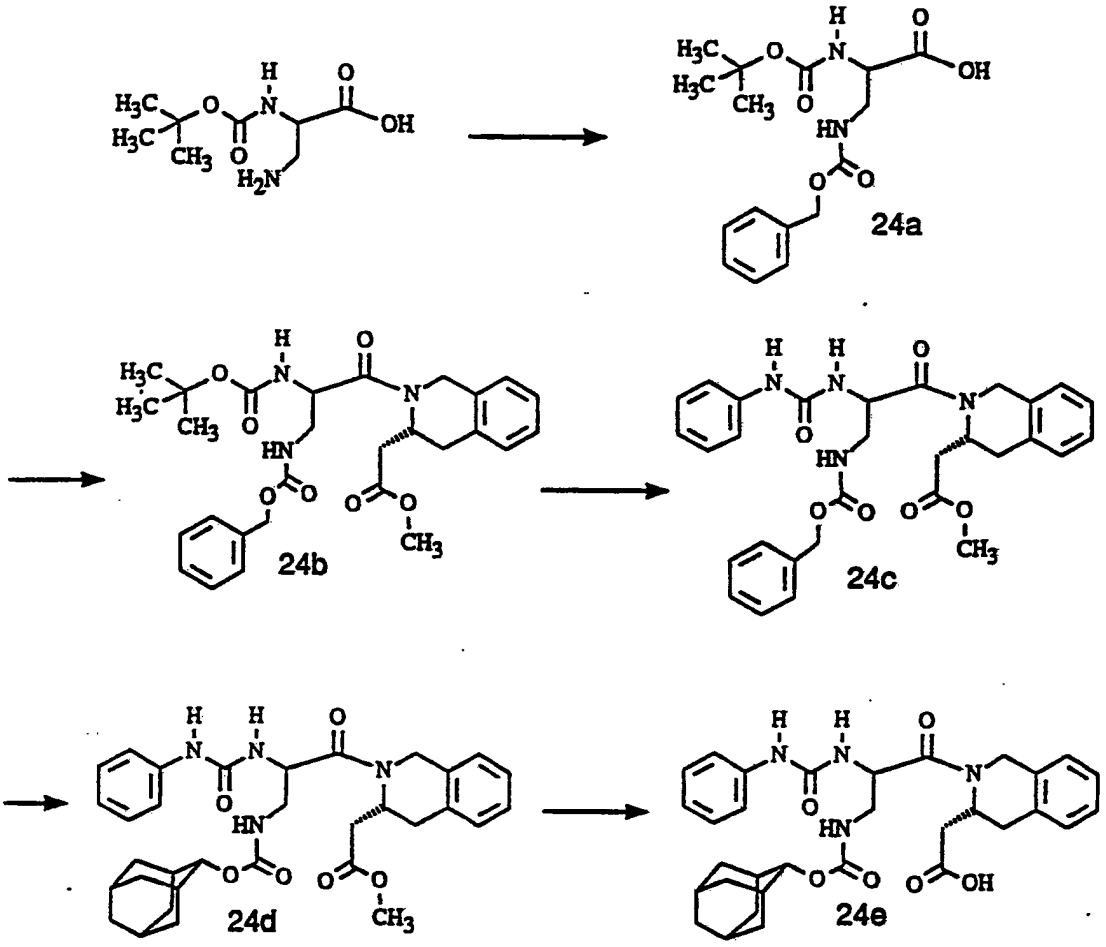
R_f (EtOAc:hexane:AcOH 50:50:1 v/v/v) 0.43

23c (3R)-2-[(S)-α-(3-Methylphenylcarbamoylamino)-cyclohexaneacetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **23b** on a 0.44 mmol scale following the method described for **1f**. The product was isolated in 57% yield (117 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 50:50:2 v/v/v).

R_f (EtOAc:hexane:AcOH 50:50:1 v/v/v) 0.21
HPLC System A t_R=14.3' >99%
Mass spec (FAB) m/e=464 $[M+H]^+$

EXAMPLE 24



24a **N^{α}-*tert*-Butyloxycarbonyl-N^{ω}-benzyloxycarbonyl-(2S)-2,3-diaminopropanoic acid.**

To a stirred ice-cold solution of N^{α}-BOC-L-diaminopropanoic acid (N. Kuchurczyk *et al*, *Synth. Commun.* **19**, 1603, 1989: 1.37 g, 6.74 mmol) in H_2O (12 mL) was added a solution of NaOH (0.64 g, 13.5 mmol) in H_2O, followed by benzyl chloroformate (1.08 mL, 7.3 mmol). The mixture was stirred and allowed to warm to room temperature over 3 hr., then the solvent was removed *in vacuo*. The residue was partitioned between EtOAc and dil $KHSO_4$, and the organic layer was washed with brine, filtered (Whatman^R

1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v) to give the title compound (1.94 g, 85%).
^{1}H NMR δ 1.15 (9H,s); 3.45 (2H,br); 4.20 (1H,br); 5.00 (2H,s); 5.7 (2H,2br); 7.1-7.3 (5H,m)

24b Methyl (3R)-2-[(2S)-3-benzyloxycarbonylamino-2-*tert*-butyloxycarbonylamino-propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1d** on a 3.3 mmol scale using **24a** instead of N-BOC-O-benzyl-threonine. The product was isolated in 76% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 50:50 v/v).
^{1}H NMR δ 1.4 (9H,2s); 3.6 (3H,2s); 7.1-7.4 (9H,m)

24c Methyl (3R)-2-[(2S)-3-(benzyloxycarbonylamino)-2-(phenylcarbamoylamino)-propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1e** on a 0.97 mmol scale using **24b** and phenylisocyanate. The product was isolated in 98% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 70:30:2 v/v/v).
R_f (EtOAc:pet. ether:AcOH 70:30:2 v/v/v) 0.37

24d Methyl (3R)-2-[(2S)-3-(2-adamantyloxycarbonylamino)-2-(phenylcarbamoylamino)-propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

To a solution of **24c** (380 mg, 0.72 mmol) in MeOH (25 mL) was added 5% Pd-on-carbon (catalytic), and hydrogen was bubbled through the mixture at room temperature/1 atm. for 2 hr. The mixture was filtered through Celite^R and the catalyst was washed with MeOH. The combined filtrates were concentrated *in vacuo*, finally with toluene azeotrope. The residue was taken up in CH_2Cl_2 (10 mL) and 2-adamantyl chloroformate (0.8 mmol) in CH_2Cl_2 (5 mL) was added dropwise with stirring, followed by diisopropylethylamine (excess). The mixture was stirred at room temperature for 12 hr. then poured into EtOAc. The solution was washed successively with 10% $KHSO_4$, satd. $KHCO_3$, H_2O and brine, filtered (Whatman^R 1PS phase separator) and concentrated *in vacuo*. The residue was used without further purification.

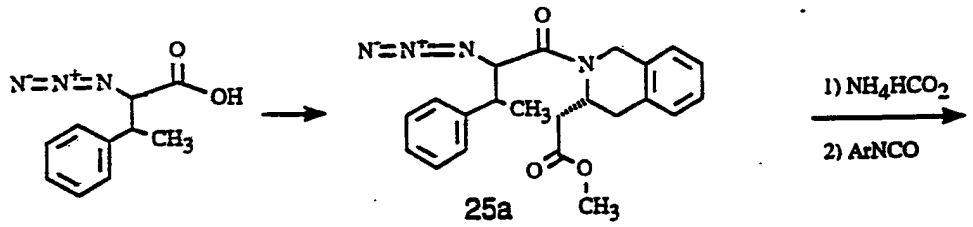
24e (3R)-2-[(2S)-3-(2-Adamantyloxycarbonylamino)-2-(phenylcarbamoylamino)-propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

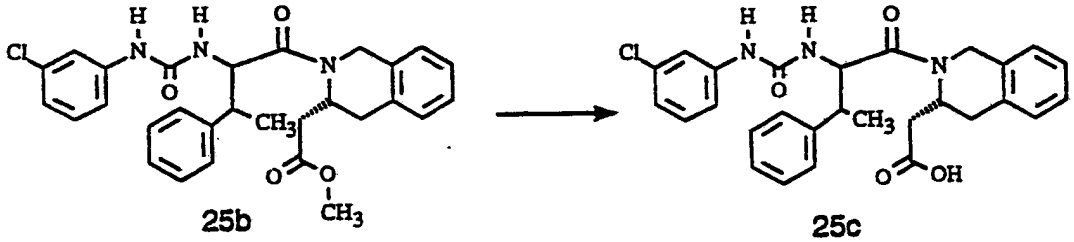
This was prepared from **24d** on a 0.21 mmol scale following the method described for 1f. The product was isolated in 52% yield (66 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System B t_R=12.5' >98%

Mass spec (FAB) m/e=575 $[M+H]^+$

EXAMPLE 25





25a Methyl (3R)-2-[(2S,3R)-2-azido-3-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for 1d on a 1.72 mmol scale using (2S,3R)-2-azido-3-phenylbutanoic acid (R. Dharanipragada *et al.*, *Tetrahedron Lett.*, **30**, 6841, 1989) instead of N-BOC-O-benzyl-threonine. The product was isolated in 62% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).

25b Methyl (3R)-2-[(2S,3R)-2-(3-chlorophenylcarbamoylamino)-3-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

To a degassed solution of **25a** (271 mg, 0.69 mmol) in $MeOH/CH_2Cl_2$ (20 mL + 3 mL) was added $NH_4^+HCO_2^-$ (174 mg, 0.28 mmol) and 5% Pd-on-carbon (50 mg). The mixture was stirred at room temperature for 5 hr. then filtered though Celite^R. The residue was washed with MeOH and the combined filtrates were concentrated *in vacuo*. The

residue was taken up in CH_2Cl_2, washed successively with 5% $KHCO_3$ and brine, dried over Na_2SO_4, and the solvent evaporated *in vacuo* to give methyl (3R)-2-[(2S,3R)-2-amino-3-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

One third of the product (*ca.* 0.23 mmol) was taken up in CH_2Cl_2 and treated with 3-chlorophenylisocyanate as described for 1e. The product was isolated in 15% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

R_f (EtOAc:pet. ether 30:70 v/v) 0.12

^1H NMR δ 1.29-1.42 (3H,m); 3.44,3.74 (3H,2s)

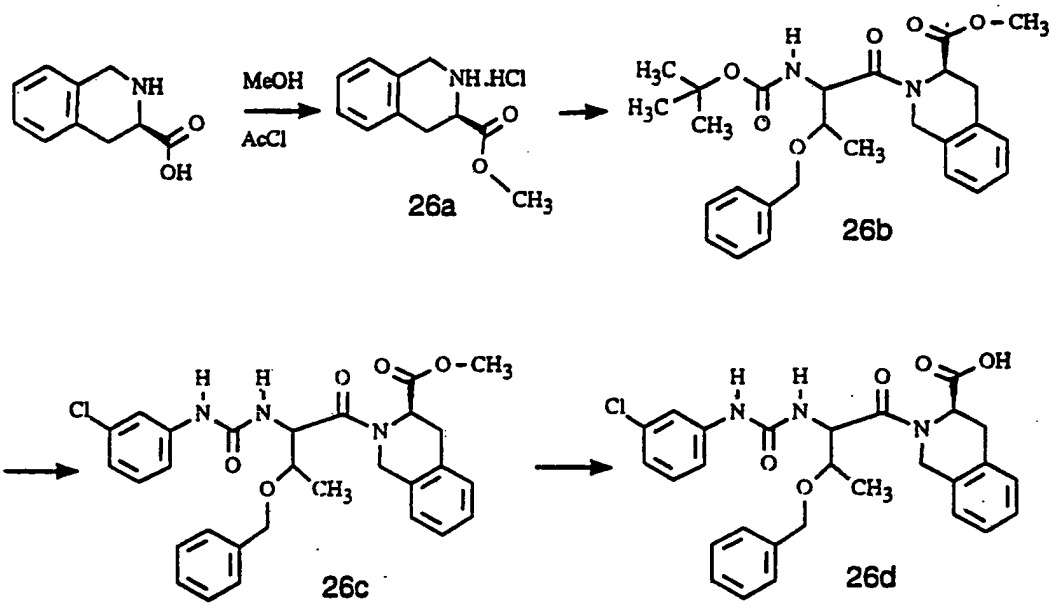
25c (3R)-2-[(2S,3R)-2-(3-Chlorophenylcarbamoylamino)-3-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **25b** on a 0.035 mmol scale following the method described for 1f. The product was isolated in 88% yield (15 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 60:40:1 v/v/v).

HPLC System B t_R=11.9' >95%

Mass spec (FAB) m/e=506 $[M+H]^+$

EXAMPLE 26



26a Methyl (3R)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate hydrochloride.

To a stirred suspension of D-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5g, 28 mmol) in MeOH (60 mL) was added acetyl chloride (3.2 mL, 45 mmol), and the mixture

was heated at reflux under N_2 for 4 hr. The solvent was removed *in vacuo*, and the residue was partitioned between EtOAc and aq. $KHCO_3$. The organic layer was washed with brine, filtered (Whatman^R 1PS phase separator), acidified with 4*N* HCl in dioxan (10 mL), and concentrated *in vacuo*. The residue was washed with pet. ether and dried over KOH to give the title compound as a white powder (3.73 g, 58%).

26b Methyl (3R)-2-[N-*tert*-butyloxycarbonyl-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared following the method described for **1d** on a 2.4 mmol scale using **26a** instead of **1c**. The product was isolated in 68% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

26c Methyl (3R)-2-[N-(3-chlorophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared following the method described for **1e** on a 0.53 mmol scale using **26b** and 3-chlorophenylisocyanate. The product was isolated in 98% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

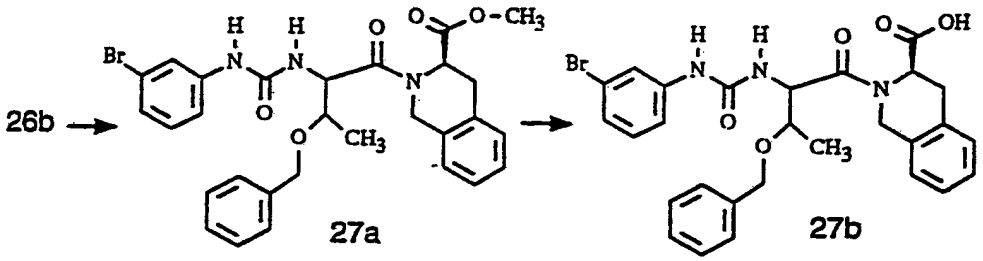
26d (3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **26c** on a 0.52 mmol scale following the method described for **1f**. The product was isolated in 32% yield (84 mg) after repeated flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v and $CHCl_3$:MeOH:AcOH 100:1:1 v/v/v).

HPLC System A t_R=16.0' >99%

Mass spec (FAB) m/e=522 $[M+H]^+$

EXAMPLE 27



27a Methyl (3R)-2-[N-(3-bromophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared following the method described for **1e** on a 0.53 mmol scale using **26b** and 3-bromophenylisocyanate. The product was isolated in 75% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

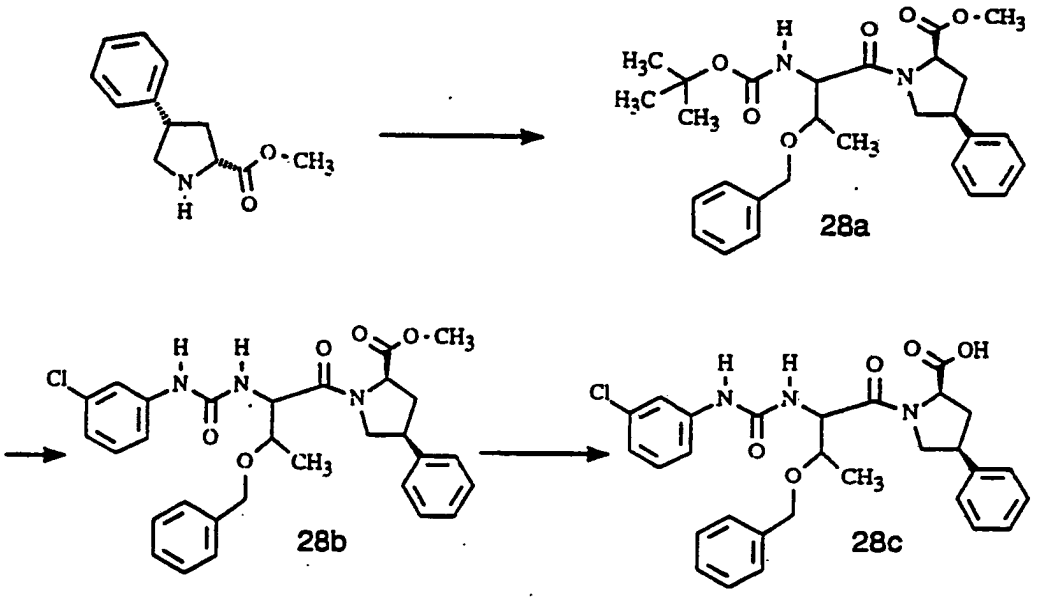
27b (3R)-2-[N-(3-Bromophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **27a** on a 0.43 mmol scale following the method described for **1f**. The product was isolated in 34% yield (82 mg) after repeated flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v and $CHCl_3$:MeOH:AcOH 100:1:1 v/v/v).

HPLC System A t_R=16.5' >99%

Mass spec (FAB) m/e=566/568 $[M+H]^+$

EXAMPLE 28



28a Methyl (2R,4S)-1-[N-*tert*-butyloxycarbonyl-O-benzyl-threonyl]-4-phenylpyrrolidine-2-carboxylate.

This was prepared following the method described for **1d** on a 0.36 mmol scale using methyl (2R,4R)-4-phenylpyrrolidine-2-carboxylate (J. Krapcho *et al*, *J.Med.Chem.*,

31.1148.1988) instead of 1c. The product was isolated in 82% yield and used without purification.

R_f (EtOAc:pet. ether 40:60 v/v) 0.30

28b Methyl (2R,4S)-1-[N-(3-chlorophenylcarbamoyl)-O-benzyl-threonyl]-4-phenylpyrrolidine-2-carboxylate.

This was prepared following the method described for 1e on a 0.30 mmol scale using 28a and 3-chlorophenylisocyanate. The product was isolated in 77% yield after flash chromatography on silica gel (eluant EtOAc:hexane 30:70 v/v).

R_f (EtOAc:pet. ether 40:60 v/v) 0.20

^1H NMR δ 1.29 (3H,d,J=6.2Hz); 3.63 (3H,s)

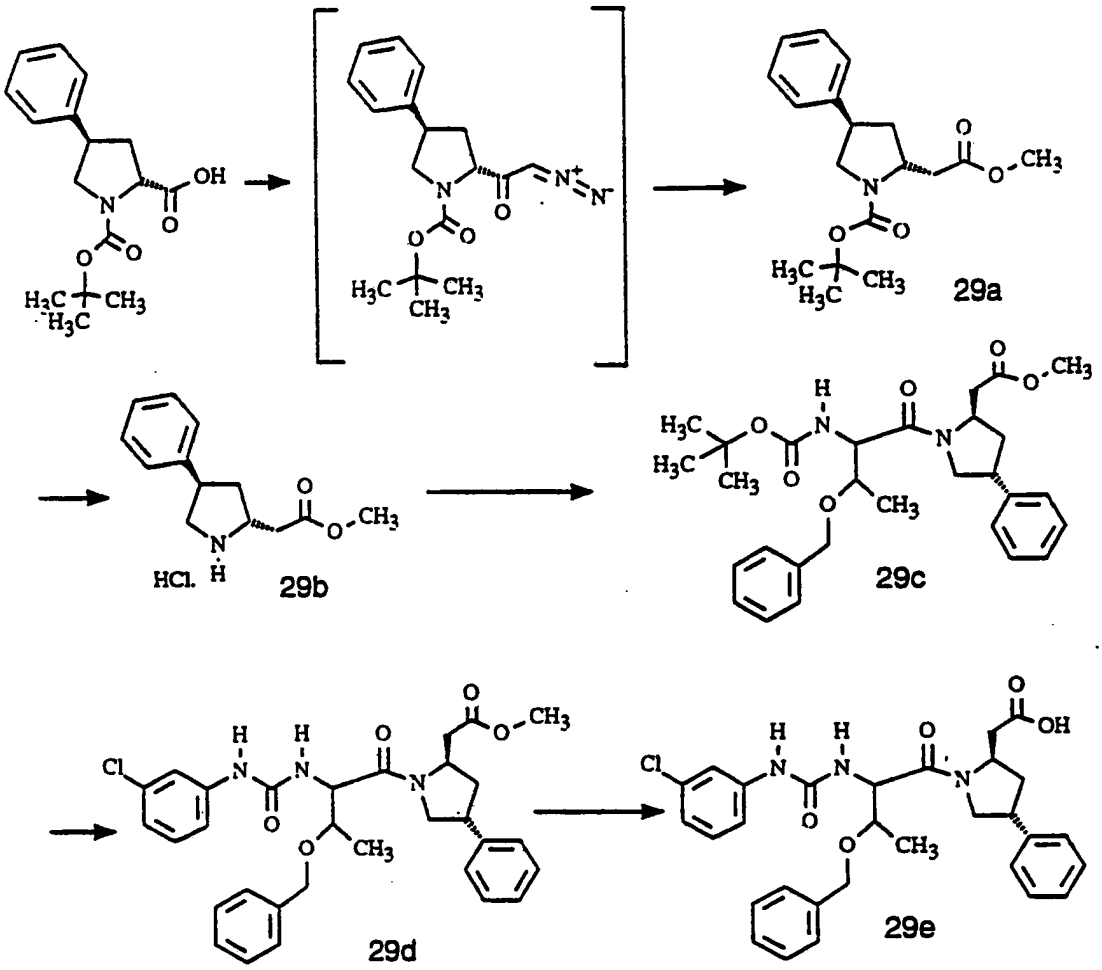
28c (2R,4S)-1-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-4-phenylpyrrolidine-2-carboxylic acid.

This was prepared from **28b** on a 0.23 mmol scale following the method described for 1f. The product was isolated in 35% yield (40 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 30:70:1 v/v/v).

HPLC System B t_R=18.2' >95%

Mass spec (FAB) m/e=536 $[M+H]^+$

EXAMPLE 29



29a Methyl (2R,4R)-1-*tert*-butyloxycarbonyl-4-phenylpyrrolidine-2-acetate.

This was prepared in a manner analogous to that used to prepare **1b** using (2R,4S)-1-*tert*-butyloxycarbonyl-4-phenylpyrrolidine-2-carboxylic acid (J. Krapcho *et al*, *J.Med.Chem.*, **31**,1148,1988: 400 mg, 1.37 mmol). The product was purified by flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v) in a yield of 64%.

29b Methyl (2R,4R)-4-phenylpyrrolidine-2-acetate hydrochloride.

This was prepared from **29a** (0.4 mmol) using the same procedure as for **1b**, assuming a yield of 100%.

29c Methyl (2R,4R)-1-[N-*tert*-butyloxycarbonyl-O-benzyl-threonyl]-4-phenylpyrrolidine-2-acetate.

This was prepared following the method described for **1d** on a 0.38 mmol scale using **29b** instead of **1c**. The product was isolated in 75% yield and used without purification.

R_f (EtOAc:pet. ether 50:50 v/v) 0.40

^1H NMR δ 1.44 (9H,s); 3.67 (3H,s)

29d Methyl (2R,4R)-1-[N-(3-chlorophenylcarbamoyl)-O-benzyl-threonyl]-4-phenylpyrrolidine-2-acetate.

This was prepared following the method described for **1e** on a 0.28 mmol scale using **29c** and 3-chlorophenylisocyanate. The product was isolated in 72% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

R_f (EtOAc:pet. ether 40:60 v/v) 0.16

^1H NMR δ 1.28 (3H,d,J=5.9Hz); 3.59 (3H,s)

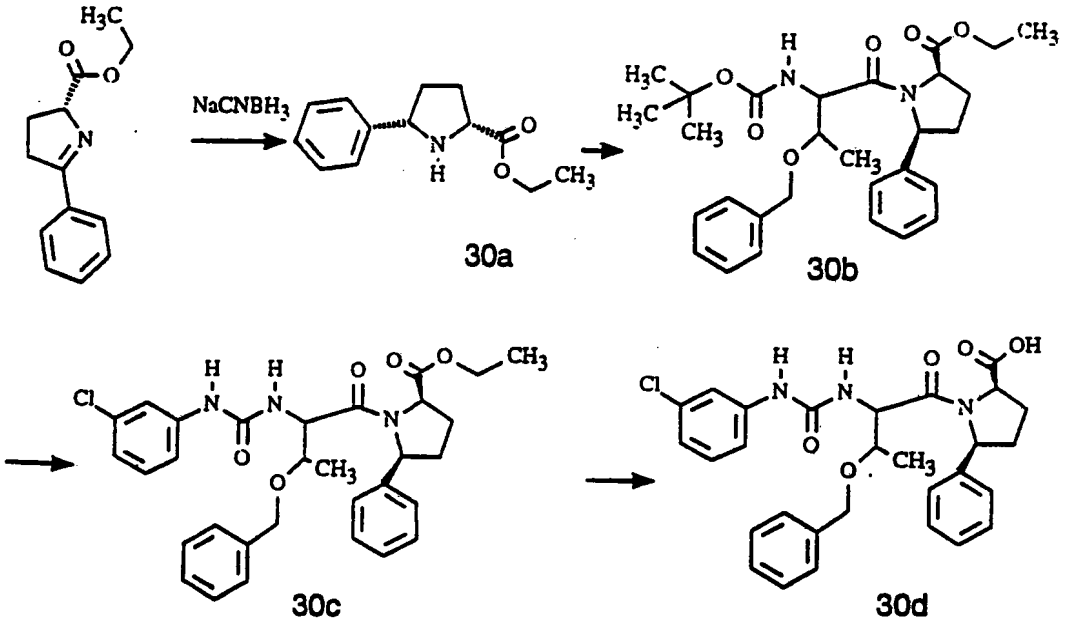
29e (2R,4R)-1-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-4-phenylpyrrolidine-2-acetic acid.

This was prepared from **29d** on a 0.20 mmol scale following the method described for **1f**. The product was isolated in 69% yield (64 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 60:40:1 v/v/v).

HPLC System B t_R=13.1' >97%

Mass spec (FAB) m/e=550 $[M+H]^+$

EXAMPLE 30



30a Ethyl (2R,5S)-5-phenylpyrrolidine-2-carboxylate.

To a solution of ethyl (2R)-3,4-dihydro-5-phenyl-2H-pyrrole-2-carboxylate (J. Ackermann *et al, Helv.Chim.Acta*, 75, 122, 1990: 1.7 g, 7.8 mmol) and AcOH (5mL) in MeOH (50 mL) was added $NaCNBH_3$ (1.5 g, 23.5 mmol). The mixture was stirred overnight at room temperature and then concentrated *in vacuo*. The residue was partitioned between EtOAc and satd. $KHCO_3$, and the organic phase was washed with H_2O and brine, filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:pet ether 25:75 then 40:60) to give the title compound (0.90 g, 40%).

30b Ethyl (2R,5S)-1-[N-*tert*-butyloxycarbonyl-O-benzyl-threonyl]-5-phenylpyrrolidine-2-carboxylate.

This was prepared following the method described for **1d** on a 0.82 mmol scale using **30a** instead of **1c**. The product was isolated in 38% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

R_f (EtOAc:hexane 30:70 v/v) 0.17

30c Ethyl (2R,5S)-1-[N-(3-chlorophenylcarbamoyl)-O-benzyl-threonyl]-5-phenylpyrrolidine-2-carboxylate.

This was prepared following the method described for 1e on a 0.31 mmol scale using 30b and 3-chlorophenylisocyanate. The product was isolated in 80% yield after flash chromatography on silica gel (eluant EtOAc:hexane 30:70 v/v).

R_f (EtOAc:hexane 30:70 v/v) 0.18

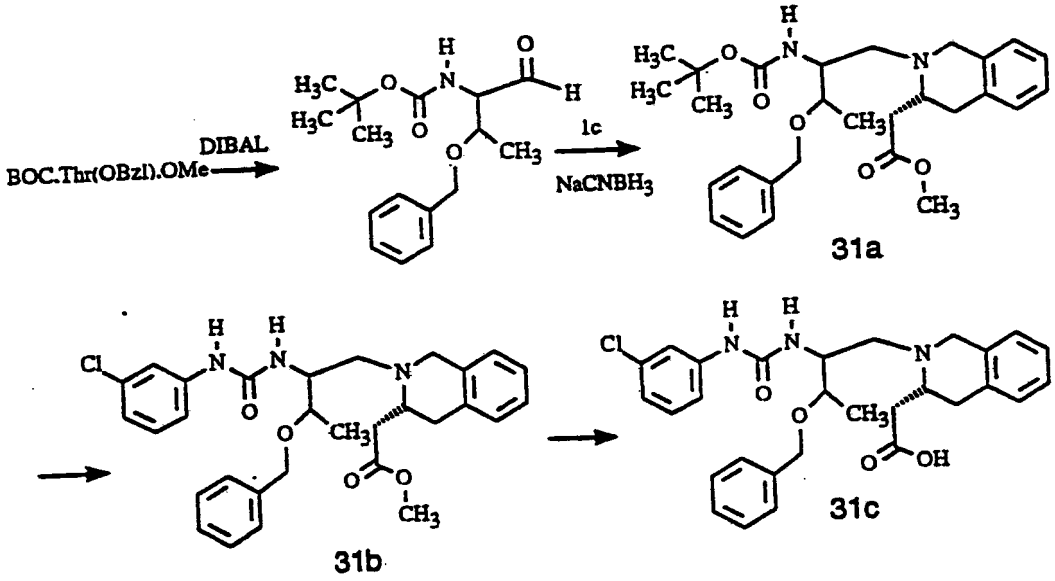
30d (2R,5S)-1-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-5-phenylpyrrolidine-2-carboxylic acid.

This was prepared from 30c on a 0.25 mmol scale following the method described for 1f. The product was isolated in 12% yield (16 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 70:30:1 v/v/v).

HPLC System A t_R=18.0' >97%

Mass spec (FAB) m/e=536 $[M+H]^+$

EXAMPLE 31



31a Methyl (3R)-2-[(2S,3R)-3-benzyloxy-2-*tert*-butyloxycarbonylamino-butyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

To a solution of N-BOC-O-benzyl-threonine methyl ester (585 mg, 1.81 mmol) in toluene (10 mL) cooled under N_2 to -78°C was added dropwise DIBAL (3.5 mL, 1.5M in toluene, 5.25 mmol). The mixture was stirred at -78°C for 40 min. then excess DIBAL was quenched by the careful addition of MeOH (1 mL). The mixture was allowed to

warm to room temperature and then poured into a vigorously stirred mixture of Et_2O and satd. Rochelle salt. The mixture was stirred for 2 hr., then the phases were separated. The aqueous layer was extracted once with Et_2O, and the combined organic phases were washed with H_2O and brine, dried over Na_2SO_4, and evaporated *in vacuo* to give N-BOC-O-benzyl-threoninal (509 mg, 96%).

A solution of this aldehyde (435 mg, 1.43 mmol) in MeOH/AcOH (99:1, 10 mL) was added at 0°C to a solution of the free base obtained from **1c** (268 mg, 1.1 mmol) in MeOH/AcOH (99:1, 10 mL). The mixture was stirred at 0°C for 15 min., then $NaCNBH_3$ (115 mg, 1.9 mmol) was added in portions over 15 min. and the mixture was stirred for a further 30 min. before being allowed to warm to room temperature. The solvent was removed *in vacuo*. The residue was taken up in EtOAc and washed successively with 10% $KHSO_4$, satd. $KHCO_3$, H_2O and brine, filtered (Whatman^R 1PS phase separator) and the solvent evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80) to give the title compound (232 mg, 41%).

31b Methyl (3R)-2-[(2S,3R)-3-benzyloxy-2-(3-chlorophenylcarbamoylamino)-butyl]-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared following the method described for **1e** on a 0.23 mmol scale using **31a** and 3-chlorophenylisocyanate. The product was isolated by flash chromatography on silica gel (eluant EtOAc:hexane 25:75 v/v).

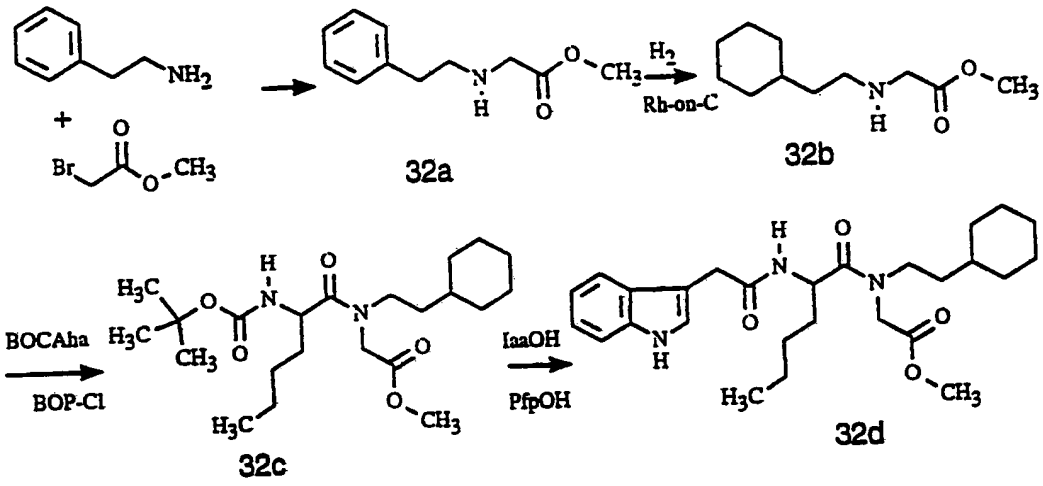
31c (3R)-2-[(2S,3R)-3-Benzyloxy-2-(3-chlorophenylcarbamoylamino)-butyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **31b** on a 0.23 mmol scale following the method described for **1f**. The product was isolated in 46% yield (55 mg) after flash chromatography on silica gel (eluant $CHCl_3$:MeOH:AcOH 40:2:1 v/v/v).

HPLC System B t_R=16.4' >98%

Mass spec (FAB) m/e=522 $[M+H]^+$

EXAMPLE 32



32a Methyl N-(phenethyl)-glycinate.

To a stirred solution of phenethylamine (2.51 mL, 20 mmol) in MeCN (50 mL) was added diisopropylethylamine (2.59 mL, 20 mmol), K_2CO_3 (1 g, excess), and methyl bromoacetate (1.9 mL, 20 mmol). The mixture was stirred at room temperature for 3 hr. and then concentrated *in vacuo*. The residue was taken up in EtOAc and the solution was washed successively with 5% $KHCO_3$, H_2O and brine, filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo* to give the title product (3.0 g, 77%) as an oil which was used without further purification.

32b Methyl N-(2-cyclohexylethyl)-glycinate.

To a solution of **32a** (55 mmol) in AcOH (100 mL) was added 5% Rh-on-carbon catalyst (0.75 g) and the mixture was shaken under H_2 (40 psi) for 7 days. The catalyst was removed by filtration, toluene was added to the filtrate, and the solvents were evaporated *in vacuo*. The residue was taken up in 1*M* HCl and washed with EtOAc. The aqueous phase was saturated with $NaHCO_3$ and extracted twice with EtOAc. The combined extracts were washed with brine, filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo* to give the title product (1.90 g, 61%) as an oil which was used without further purification.

32c Methyl N-(2-cyclohexylethyl)-N-((2S)-2-(*tert*-butyloxycarbonylamino)-hexanoyl)-glycinate.

To a stirred solution of (2S)-2-*tert*-butyloxycarbonylaminohexanoic acid (978 mg, 4.2 mmol) in CH_2Cl_2 was added diisopropylethylamine (0.74 mL, 4.2 mmol). The solution was cooled to -20°C and BOP-Cl (1.08 g, 4.2 mmol) was added. The solution was stirred at 20°C for 20 min., then amine **32b** (0.60 g, 3.03 mmol) was added and the mixture was allowed to warm to room temperature. The mixture was stirred at room temperature for 16 hr. then the solvent was evaporated *in vacuo*. The residue was taken up in EtOAc and the solution was washed with 0.3*M* $KHSO_4$, satd. $KHCO_3$, H_2O and brine, filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:hexane 25:75 v/v) to give the title compound (310 mg, 24%).

R_f (EtOAc:hexane 25:75 v/v) 0.16

32d Methyl N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycinate.

A solution of the BOC-protected compound **32c** (310 mg, 0.75 mmol) in 4*N* HCl in dioxan (20 mL) was stirred at room temperature for 1 hr then concentrated *in vacuo*, finally with toluene azeotrope.

Meanwhile, to a stirred solution of 3-indoleacetic acid (184 mg, 1.05 mmol) and pentafluorophenol (202 mg, 1.1 mmol) in CH_2Cl_2 (10 mL), cooled to 0°C, was added water-soluble carbodiimide (WSCD.HCl, Peptide Inst. Inc., 287 mg, 1.5 mmol). The mixture was stirred at 0°C for 1 hr, then the residue from the above HCl deprotection was added, followed by diisopropylethylamine (0.13 mL, 0.75 mmol) and the mixture was stirred at room temperature overnight. The solvent was removed *in vacuo*, and the residue was taken up in EtOAc. The solution was washed with 0.3*M* $KHSO_4$, satd. $KHCO_3$, H_2O and brine, filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 55:45:1 v/v/v) to give the title compound (148 mg, 42%). A part of this was taken up in MeCN/H2O and lyophilised.

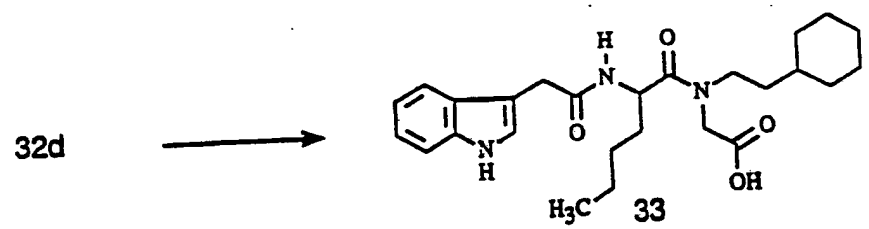
R_f (EtOAc:hexane:AcOH 50:50:1 v/v/v) 0.17

HPLC System A t_R=18.8' >98%

AAA Peptide content=80%

Mass spec (FAB) m/e=470 $[M+H]^+$

EXAMPLE 33



33 N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycine.

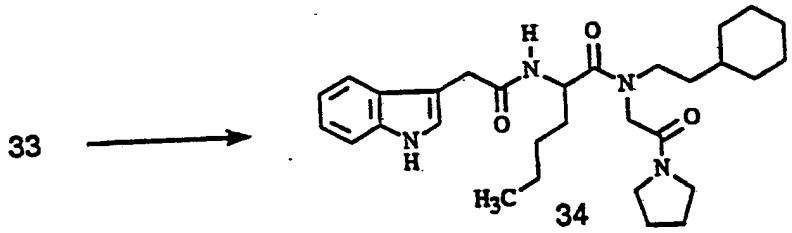
This was prepared from 32d on a 0.35 mmol scale following the method described for 1f. The product was isolated in 53% yield (85 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 75:25:2 v/v/v).

HPLC System A t_R=14.6' >99%

AAA Peptide content=76%

Mass spec (FAB) m/e=455 $[M+Na]^+$

EXAMPLE 34



34 1-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-pyrrolidine.

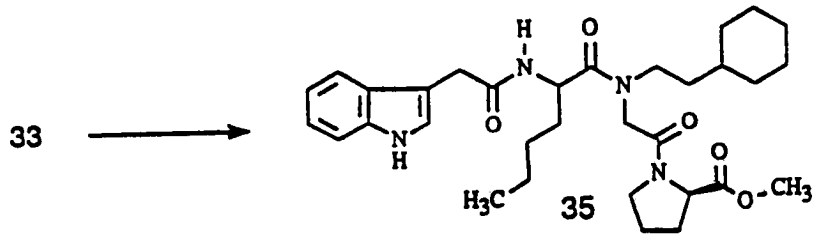
To a stirred solution of 33 (86 mg, 0.19 mmol) and hydroxybenzotriazole (33 mg, 0.25 mmol) in CH_2Cl_2 (8 mL), cooled to 0°C, was added WSCD.HCl (73 mg, 0.38 mmol). The mixture was stirred at 0°C for 1 hr., then pyrrolidine (50 µL, 0.57 mmol) was added. The mixture was stirred at 0°C for a further 2 hrs. then at room temperature overnight. The solvent was removed *in vacuo*, and the residue was taken up in EtOAc. The solution was washed with 0.3*M* $KHSO_4$, satd. $KHCO_3$, H_2O and brine, filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v) and lyophilised from MeCN/H_2O to give the title compound (36 mg, 36%).

HPLC System A t_R=17.8' >98%

AAA Peptide content=80%

Mass spec (FAB) m/e=509 $[M+H]^+$

EXAMPLE 35



35 Methyl N-{N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-prolinate.

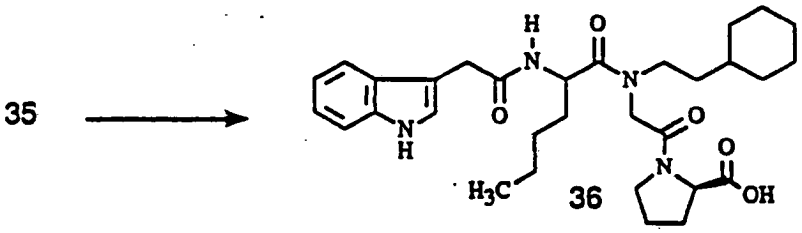
This was prepared from 33 on a 0.27 mmol scale following the method described for 34 using D-ProOMe instead of pyrrolidine. The product was isolated in 68% yield (105 mg) after flash chromatography on silica gel (eluant EtOAc:hexane 95:5 v/v).

HPLC System A t_R=14.1' >80%

AAA Aha 0.99; Pro 1.01; Peptide content=76%

Mass spec (FAB) m/e=567 $[M+H]^+$

EXAMPLE 36



36 N-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-proline.

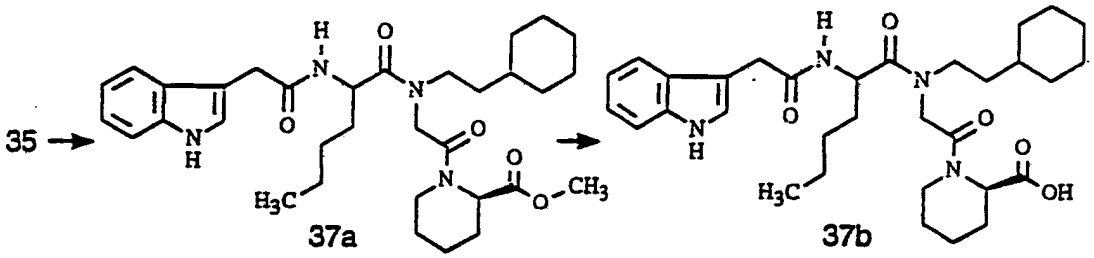
This was prepared from 35 on a 0.21 mmol scale following the method described for 1f. The product was isolated in 45% yield (51 mg) after flash chromatography on silica gel (eluant $CHCl_3$:MeOH:AcOH 40:2:1 v/v/v).

HPLC System A t_R=15.4' >99%

AAA Aha 1.00; Pro 1.00; Peptide content=72%

Mass spec (FAB) m/e=552 $[M+K]^+$

EXAMPLE 37



37a Methyl N-{N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-pipecolate.

This was prepared from 33 on a 0.27 mmol scale following the method described for 34 using methyl D-pipecolate instead of pyrrolidine. The product was isolated in 85% yield after flash chromatography on silica gel (eluant EtOAc:hexane 85:15 v/v).

R_f (EtOAc:hexane 95:5 v/v) 0.32

37b N-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-pipecolic acid.

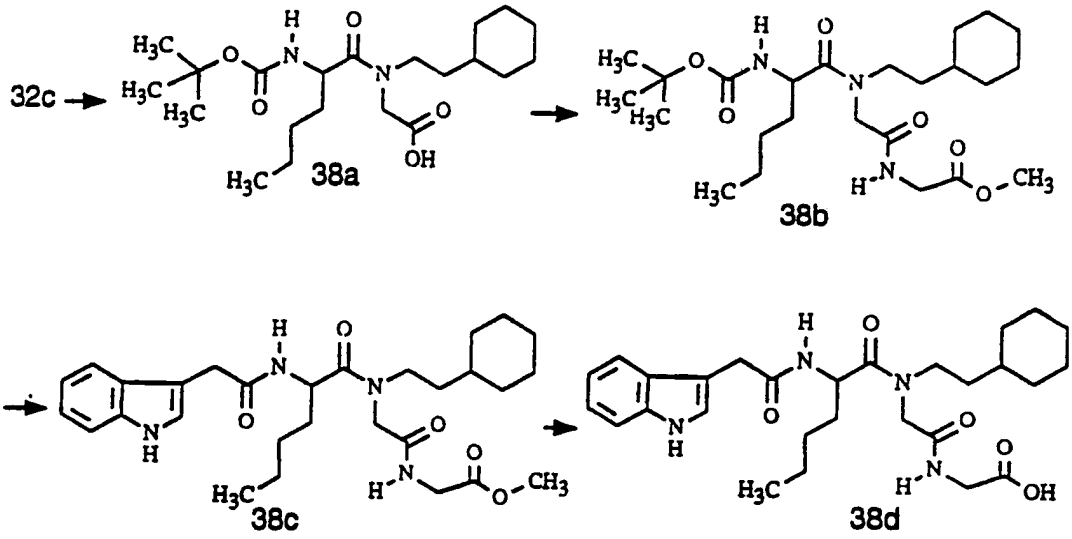
This was prepared from 37a on a 0.17 mmol scale following the method described for 1f. The product was isolated in 10% yield (10 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System A t_R=17.6' >80%

AAA Peptide content=74%

Mass spec (FAB) m/e=567 $[M+H]^+$

EXAMPLE 38



38a N-(2-Cyclohexylethyl)-N-((2S)-2-(*tert*-butyloxycarbonylamino)-hexanoyl)-glycine.

This was prepared from **32c** on a 1.82 mmol scale following the method described for **1f**. The product was used without purification, assuming a yield of 100%.

38b Methyl N-{N-(2-cyclohexylethyl)-N-((2S)-2-(*tert*-butyloxycarbonylamino)-hexanoyl)-glycyl}-glycinate.

This was prepared from **38a** on a 0.91 mmol scale following the method described for **34** using GlyOMe instead of pyrrolidine. The product was used without purification, assuming a yield of 100%.

R_f (EtOAc:pet. ether 75:25 v/v) 0.59

38c Methyl N-{N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-glycinate.

This was prepared from **38b** on a 0.91 mmol scale following the method described for **32d** using hydroxybenzotriazole instead of pentafluorophenol. The product was isolated in 44% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 50:50 v/v then neat EtOAc).

38d N-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-glycine.

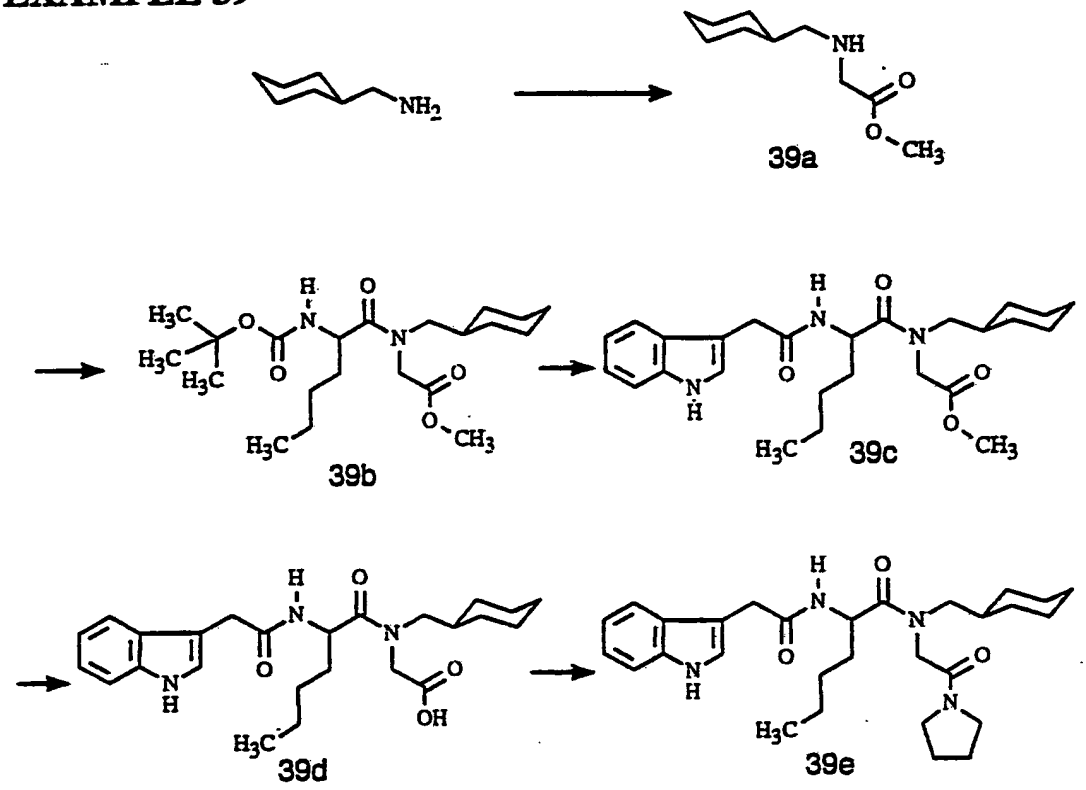
This was prepared from 38c on a 0.40 mmol scale following the method described for 1f. The product was isolated in 49% yield (105 mg) after flash chromatography on silica gel (eluant EtOAc:MeOH:AcOH 100:4:4 v/v/v).

HPLC System A t_R=10.0' >98%

AAA Peptide content=79%

Mass spec (FAB) m/e=535 $[M+Na]^+$

EXAMPLE 39



39a Methyl N-(cyclohexylmethyl)-glycinate.

This was prepared from cyclohexylmethylamine on a 3.0 mmol scale following the method described for 32a. The product was used without purification, assuming a yield of 100%.

39b Methyl N-(cyclohexylmethyl)-N-((2S)-2-(*tert*-butyloxycarbonylamino)-hexanoyl)-glycinate.

This was prepared from **39a** on a 3.0 mmol scale following the method described for **32c**. The product was isolated in 52% yield after flash chromatography on silica gel (eluant EtOAc:hexane 25:75 v/v).

R_f (EtOAc:hexane 25:75 v/v) 0.23

39c Methyl N-(cyclohexylmethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycinate.

This was prepared from **39b** on a 1.6 mmol scale following the method described for **32d**. The product was isolated in 69% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 50:50:1 v/v/v).

R_f (EtOAc:hexane:AcOH 50:50:1 v/v/v) 0.20

39d N-(Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycine.

This was prepared from **39c** on a 1.1 mmol scale following the method described for **1f**. The product was isolated in 22% yield after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

R_f (EtOAc:AcOH 100:2 v/v) 0.18

39e 1-{N-(2-Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-pyrrolidine.

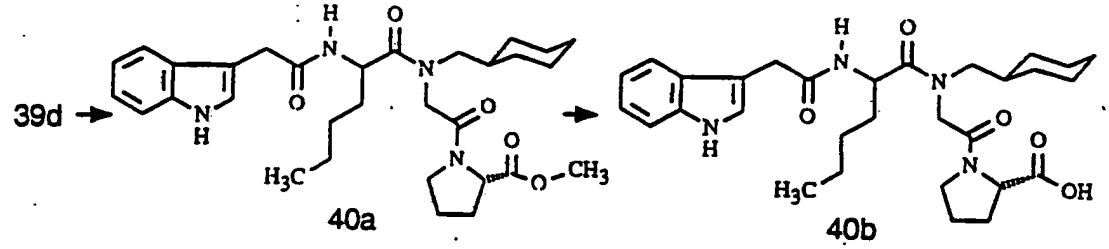
This was prepared from **39d** on a 0.48 mmol scale following the method described for **34**. The product was isolated in 44% yield (109 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System A t_R=15.4' >99%

AAA Peptide content=83%

Mass spec (FAB) m/e=495 $[M+H]^+$

EXAMPLE 40



40a Methyl 1-{N-(2-cyclohexylmethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-prolinate.

This was prepared from **39d** on a 0.23 mmol scale following the method described for **34** using ProOMe instead of pyrrolidine. The product was isolated in 72% yield after flash chromatography on silica gel (eluant EtOAc).

R_f (EtOAc:hexane 90:10 v/v) 0.14

40b 1-{N-(2-Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-proline.

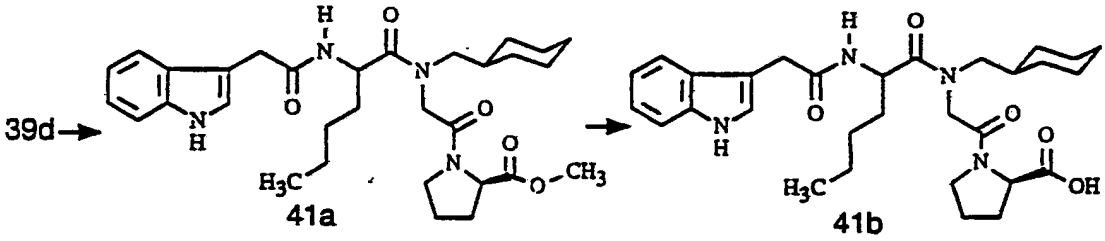
This was prepared from **40a** on a 0.16 mmol scale following the method described for **1f**. The product was isolated in 45% yield (38 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System A t_R=11.8' >99%

AAA Aha 1.01; Pro 0.99; Peptide content=81%

Mass spec (FAB) m/e=561 $[M+Na]^+$

EXAMPLE 41



41a Methyl 1-{N-(2-Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-prolinate.

This was prepared from **39d** on a 0.23 mmol scale following the method described for **34** using D-ProOMe instead of pyrrolidine. The product was isolated in 48% yield after flash chromatography on silica gel (eluant EtOAc).

R_f (EtOAc:hexane 90:10 v/v) 0.14

41b 1-{N-(2-Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-proline.

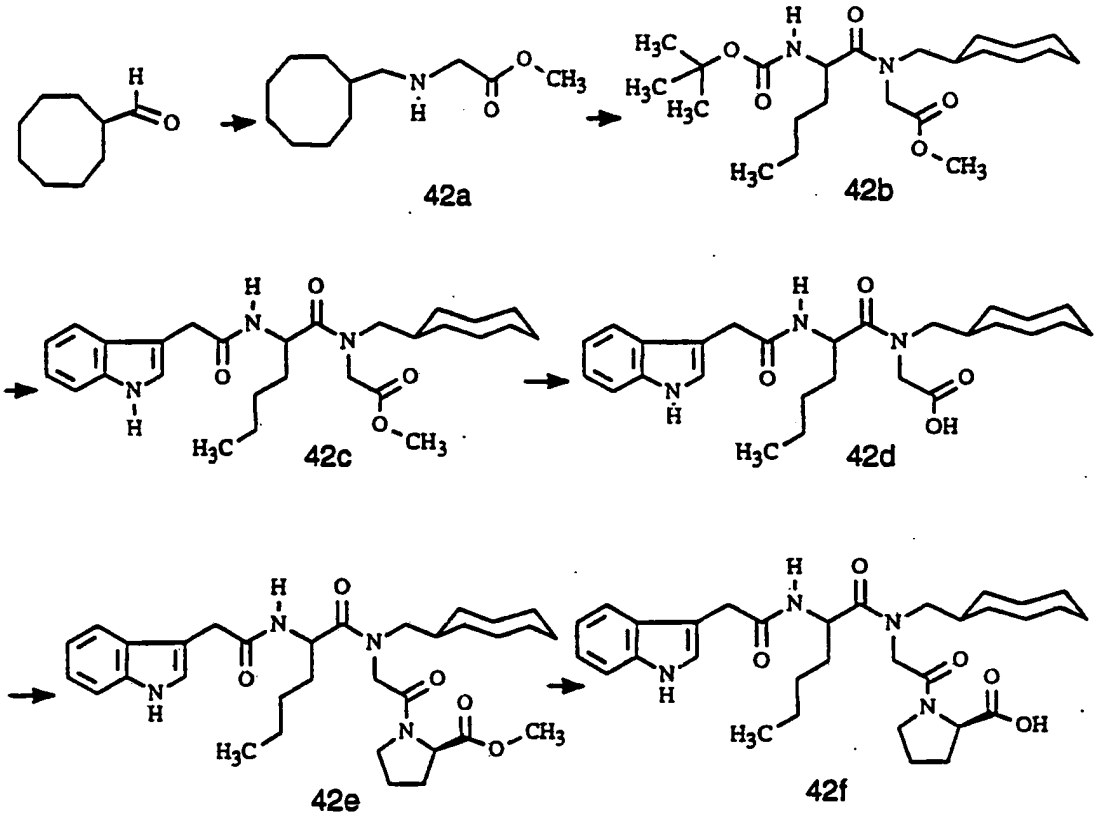
This was prepared from **41a** on a 0.11 mmol scale following the method described for 1f. The product was isolated in 52% yield (30 mg) after flash chromatography on silica gel (eluant CHCl3:MeOH:AcOH 40:2:1 v/v/v).

HPLC System A t_R=12.1' >99%

AAA Aha 0.98: Pro 1.02; Peptide content=84%

Mass spec (FAB) m/e=561 $[M+Na]^+$

EXAMPLE 42



42a Methyl N-(cyclooctylmethyl)-glycinate.

To a stirred solution of cyclooctanecarboxaldehyde (0.70 g, 5 mmol) and GlyOMe.HCl (0.75 g, 6 mmol) in MeOH (50 mL) at room temperature was added AcOH (2 mL), diisopropylethylamine (1.04 mL, 6 mmol) and $NaCNBH_3$ (0.75 g, 12 mmol). The mixture was stirred at room temperature for 4 hr., then the solvent was evaporated *in vacuo* and the residue was partitioned between EtOAc and satd. $KHCO_3$. The organic

phase was washed with H_2O and brine, filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc) to give the title compound (500 mg, 47%).

R_f (EtOAc) 0.47

^1H NMR δ 2.42 (2H,d,J=6Hz); 3.35 (2H,s); 3.68 (3H,s)

42b Methyl N-(cyclooctylmethyl)-N-((2S)-2-(*tert*-butyloxycarbonylamino)-hexanoyl)-glycinate.

This was prepared from **42a** on a 2.35 mmol scale following the method described for **32c**. The product was isolated in 99% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75).

R_f (EtOAc:pet. ether 25:75 v/v) 0.41

42c Methyl N-(cyclooctylmethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycinate.

This was prepared from **42b** on a 2.35 mmol scale following the method described for **38c**. The product was isolated in 79% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 50:50 v/v).

R_f (EtOAc:pet. ether 65:35 v/v) 0.46

HPLC System A t_R=16.3'

^1H NMR Major rotamer δ 4.45 (1H,d,J=17Hz); 5.15 (1H,m)

Minor rotamer δ 4.15 (1H,d,J=17Hz); 4.55 (1H,d,J=17Hz); 4.90 (1H,m)

Mass spec (FAB) m/e=484 $[M+H]^+$

42d N-(Cyclooctylmethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycine.

This was prepared from **42c** on a 1.86 mmol scale following the method described for **1f**. The product was used without puification, assuming a yield of 100%.

HPLC System A t_R=12.6'

Mass spec (FAB) m/e=470 $[M+H]^+$

42e Methyl 1-{N-(cyclooctylmethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-prolinate.

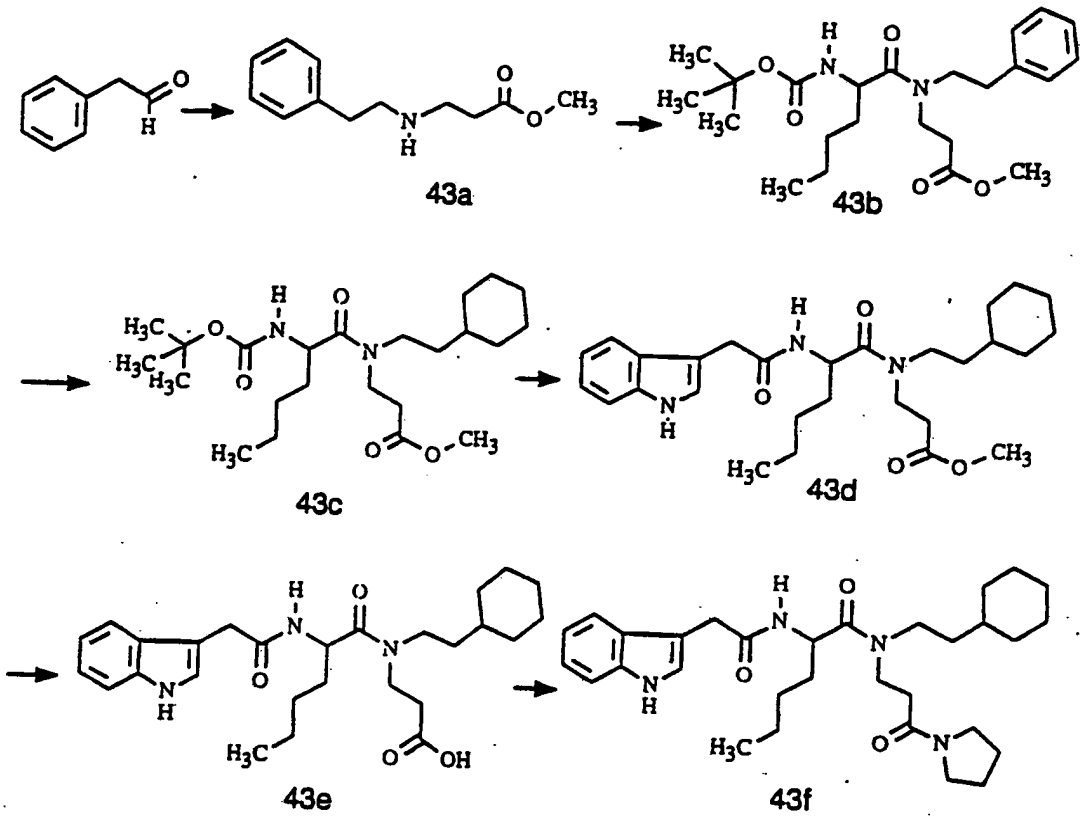
This was prepared from **42d** on a 1.49 mmol scale following the method described for **33** using D-ProOMe instead of pyrrolidine. The product was isolated in 50% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 80:20 v/v).

HPLC System A t_R=14.8'
Mass spec (FAB) m/e=581 $[M+H]^+$

42f 1-{N-(Cyclooctylmethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-proline.

This was prepared from 42e on a 0.62 mmol scale following the method described for 1f. The product was isolated in 79% yield (276 mg) without purification.
HPLC System A t_R=12.0' >98%
AAA Aha 1.01; Pro 0.99: Peptide content=84%
Mass spec (FAB) m/e=567 $[M+H]^+$

EXAMPLE 43



43a Methyl 3-(phenethylamino)-propanoate.

This was prepared from phenylacetaldehyde and β-AlaOMe on a 5.0 mmol scale following the method described for 42a. The product was isolated in 68% yield and used without further purification.

43b Methyl 3-{N-(phenethyl)-N-((2S)-2-(*tert*-butyloxycarbonylamino)-hexanoyl)-amino}-propanoate.

This was prepared from **43a** on a 3.4 mmol scale following the method described for **32c**. The product was isolated in 42% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

43c Methyl 3-{N-(2-cyclohexylethyl)-N-((2S)-2-(*tert*-butyloxycarbonylamino)-hexanoyl)-amino}-propanoate.

This was prepared from **43b** on a 1.43 mmol scale following the method described for **32b**. After evaporating the solvent the product was taken up in EtOAc and washed with satd. $KHCO_3$, H_2O and brine, filtered (Whatman^R 1PS phase separator), and the solvent removed *in vacuo*. The product was used without further purification, assuming a yield of 100%.

43d Methyl 3-{N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-amino}-propanoate.

This was prepared from **43c** on a 1.43 mmol scale following the method described for **38c**. The product was isolated in 64% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 65:35 v/v).

43e 3-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-amino}-propanoic acid.

This was prepared from **43d** on a 0.91 mmol scale following the method described for **1f**. The product was isolated in 66% yield after flash chromatography (eluant EtOAc:pet.ether:AcOH 80:20:2 v/v/v).

HPLC System A t_R=12.3'

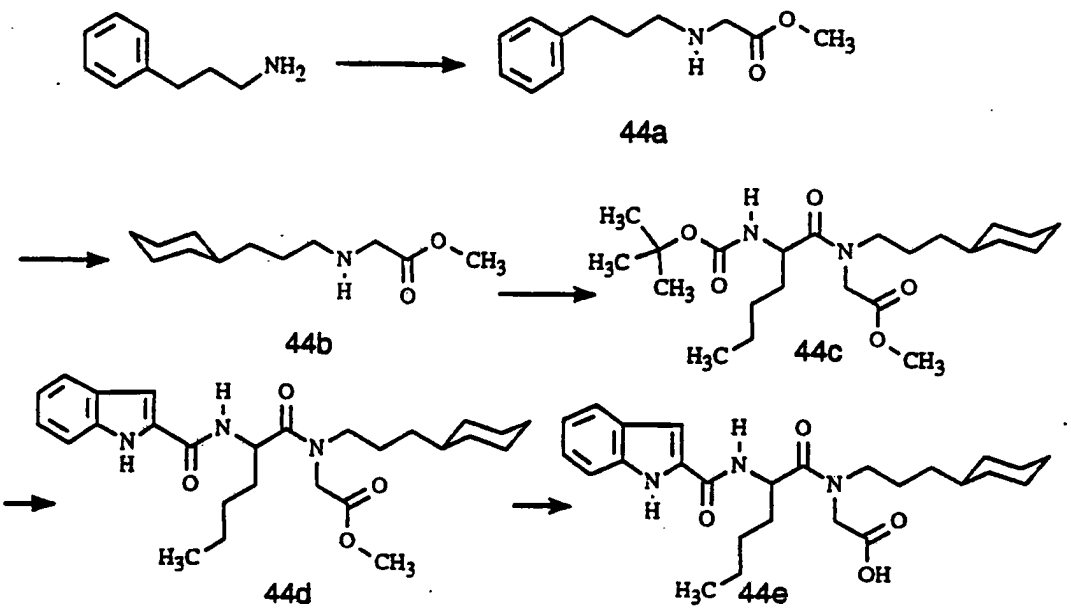
Mass spec (FAB) m/e=470 $[M+H]^+$

43f 1-{3-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-amino}-propanoyl}-pyrrolidine.

This was prepared from **43e** on a 0.50 mmol scale following the method described for **33**. The product was isolated in 50% yield (95 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System A t_R=14.2' >98%
AAA Peptide content=79%
Mass spec (FAB) m/e=523 $[M+H]^+$

EXAMPLE 44



44a Methyl N-(3-phenylpropyl)-glycinate.

This was prepared from 3-phenylpropylamine on a 20 mmol scale following the method described for **32a**. The product was used without purification assuming a yield of 100%.

44b Methyl N-(3-cyclohexylpropyl)-glycinate.

This was prepared from **44a** on a 20 mmol scale following the method described for **32b**. The product was isolated in a yield of 69% and used without further purification.
^{1}H NMR δ 2.50 (2H,t,J=7Hz); 3.34 (2H,s); 3.81 (3H,s)

44c Methyl N-(3-cyclohexylpropyl)-N-((2S)-2-(*tert*-butyloxycarbonylamino)-hexanoyl)-glycinate.

This was prepared from **44b** on a 5.8 mmol scale following the method described for **32c**. The product was isolated in 68% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

44d Methyl N-(3-cyclohexylpropyl)-N-((2S)-2-(2-indolecarbonylamino)-hexanoyl)-glycine.

This was prepared from **44c** on a 0.59 mmol scale following the method described for **38c**. The product was isolated in 90% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

^{1}H NMR Major rotamer δ 3.64 (1H,d,J=17Hz); 4.21 (1H,d,J=17Hz); 5.05 (1H,m)

Minor rotamer δ 3.85 (1H,d,J=17Hz); 4.21 (1H,d,J=17Hz); 4.80 (1H,m)

44e N-(3-Cyclohexylpropyl)-N-((2S)-2-(2-indolecarbonylamino)-hexanoyl)-glycine.

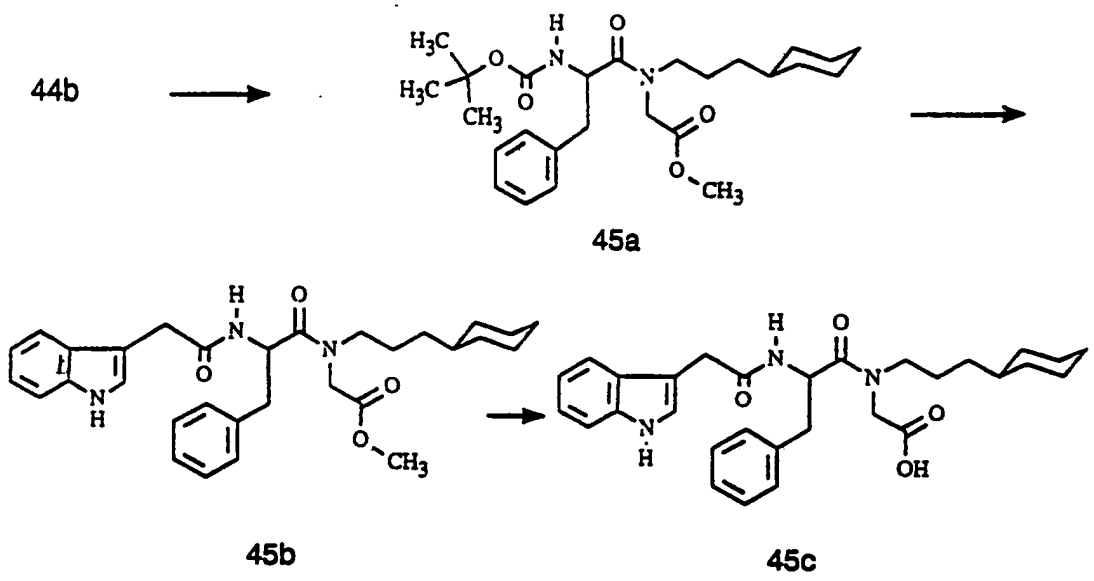
This was prepared from **44d** on a 0.53 mmol scale following the method described for **1f**. The product was isolated in 66% yield (120 mg) after flash chromatography (eluant EtOAc:pet.ether:AcOH 60:40:2 v/v/v).

HPLC System A t_R=16.9' >98%

AAA Peptide content=81%

Mass spec (FAB) m/e=456 $[M+H]^+$

EXAMPLE 45



45a Methyl N-(3-cyclohexylpropyl)-N-(N-(*tert*-butyloxycarbonyl)-phenylalanyl)-glycinate.

This was prepared from **44b** on a 2.9 mmol scale following the method described for **32c** using BOC-Phe instead of BOC-aminohexanoic acid. The product was isolated in 77% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

45b Methyl N-(3-cyclohexylpropyl)-N-(N-(3-indoleacetyl)-phenylalanyl)-glycinate.

This was prepared from **45a** on a 2.4 mmol scale following the method described for **38c**. The product was isolated in 28% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 70:30 v/v).

45c N-(3-Cyclohexylpropyl)-N-(N-(3-indoleacetyl)-phenylalanyl)-glycine.

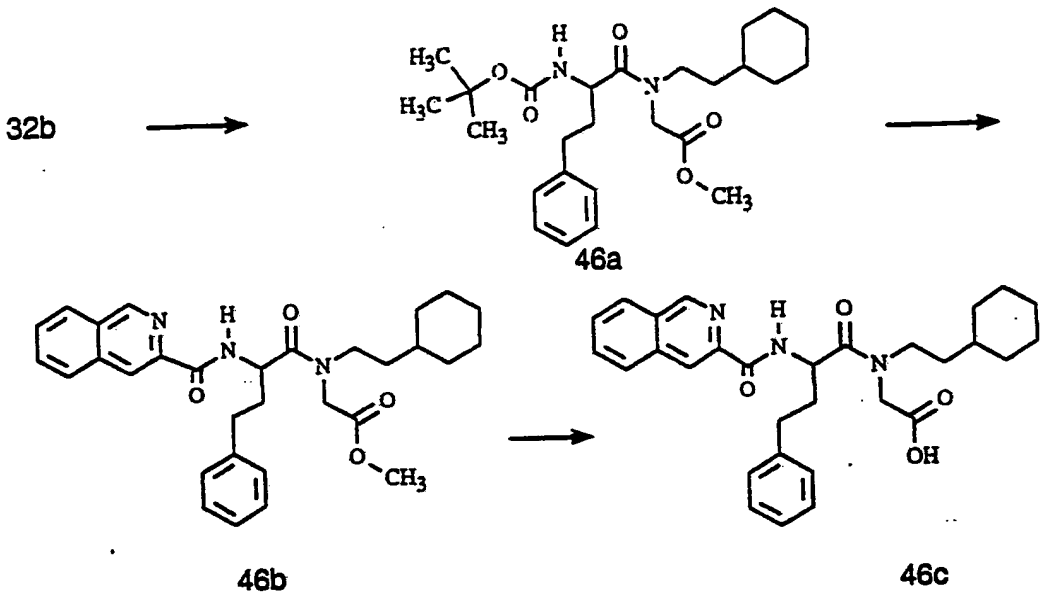
This was prepared from **45b** on a 0.68 mmol scale following the method described for **1f**. The product was isolated in 46% yield (159 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System A t_R=14.6' >95%

AAA Peptide content=86%

Mass spec (FAB) m/e=504 $[M+H]^+$

EXAMPLE 46



46a Methyl N-(2-cyclohexylethyl)-N-((2S)-2-(*tert*-butyloxycarbonylamino)-4-phenylbutanoyl)-glycinate.

This was prepared from **32b** on a 4.8 mmol scale following the method described for **32c** using BOC-amino-4-phenylbutanoic acid instead of BOC-aminohexanoic acid. The product was isolated in 79% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

46b . Methyl N-(2-cyclohexylethyl)-N-((2S)-2-(3-isoquinolinecarbonylamino)-4-phenylbutanoyl)-glycinate.

This was prepared from **46a** on a 0.75 mmol scale following the method described for **32c** using 3-isoquinolinecarboxylic acid instead of 3-indoleacetic acid. The product was isolated in 62% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

46c N-(2-Cyclohexylethyl)-N-((2S)-2-(3-isoquinolinecarbonylamino)-4-phenylbutanoyl)-glycine.

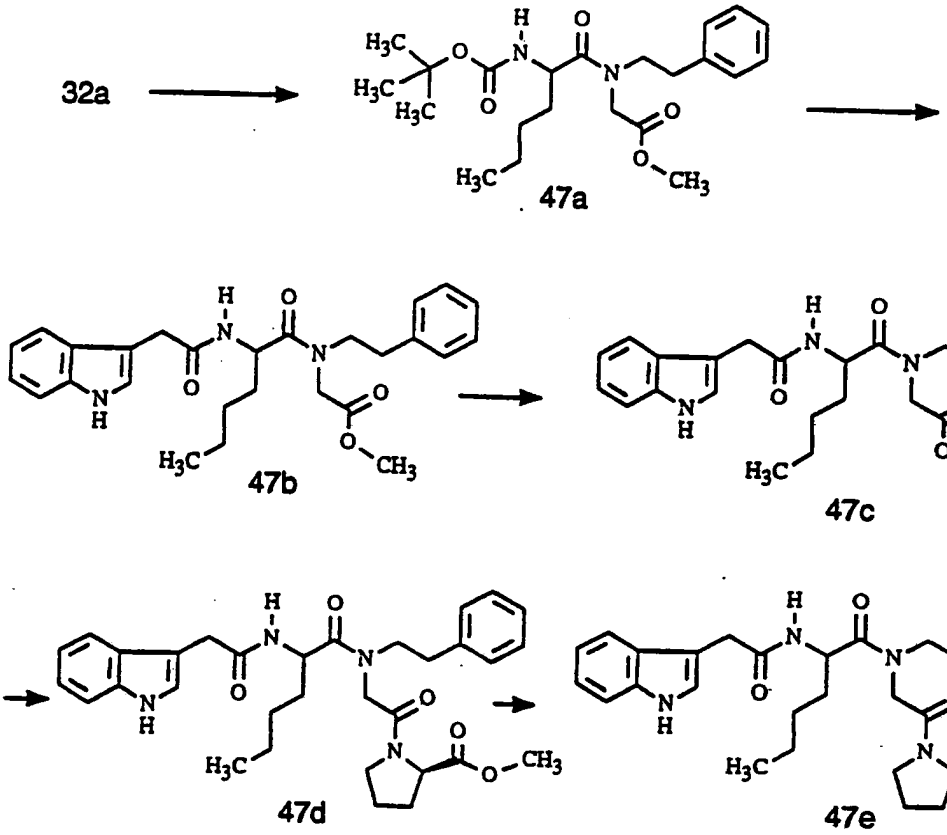
This was prepared from **46b** on a 0.47 mmol scale following the method described for **1f**. The product was isolated in 52% yield (121 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System A t_R=17.2' >99%

AAA Peptide content=97%

Mass spec (FAB) m/e=502 $[M+H]^+$

EXAMPLE 47



47a Methyl N-phenethyl-N-((2S)-2-(*tert*-butyloxycarbonylamino)-hexanoyl)-glycinate.

This was prepared from **32a** on a 2.6 mmol scale following the method descibed for **32c**. The product was isolated in 75% yield after flash chromatography on silica gel (eluant EtOAc:hexane 25:75 v/v).

R_f (EtOAc:hexane 40:60 v/v) 0.35

47b Methyl N-phenethyl-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycinate.

This was prepared from **47a** on a 1.2 mmol scale following the method descibed for **32d**. The product was isolated in 71% yield after flash chromatography on silica gel (eluant EtOAc:hexane 70:30 v/v).

R_f (EtOAc:hexane 70:30 v/v) 0.16

47c N-Phenethyl-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycine.

This was prepared from **47b** on a 0.88 mmol scale following the method descibed for **1f**. The product was isolated in 70% yield after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

R_f (EtOAc:AcOH 100:2 v/v) 0.21

47d Methyl N-{N-phenethyl-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-prolinate.

This was prepared from **47c** on a 0.22 mmol scale following the method descibed for **34** using D-ProOMe instead of pyrrolidine. The product was isolated in 50% yield after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

R_f (EtOAc:AcOH 100:2 v/v) 0.16

47e N-{N-Phenethyl-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-proline.

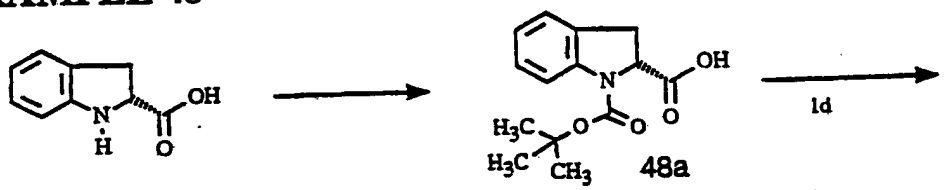
This was prepared from **47d** on a 0.11 mmol scale following the method descibed for **1f**. The product was isolated in 38% yield (23 mg) after flash chromatography on silica gel (eluant $CHCl_3$:MeOH:AcOH 35:2:1 v/v/v).

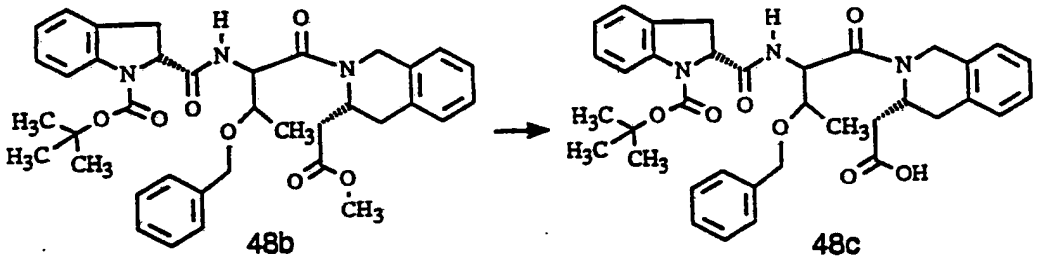
HPLC System A t_R=11.2' >98%

AAA Aha 0.99; Pro 1.01: Peptide content=65%

Mass spec (FAB) m/e=569 $[M+H]^+$

EXAMPLE 48





48a 1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from (2R)-2,3-dihydroindole-2-carboxylic acid (M. Vincent *et al. Tetrahedron Lett.*, **23**, 1677, 1982) on a 65 mmol scale following the method described for **1a**. The product was isolated in 98% yield and used without further purification.

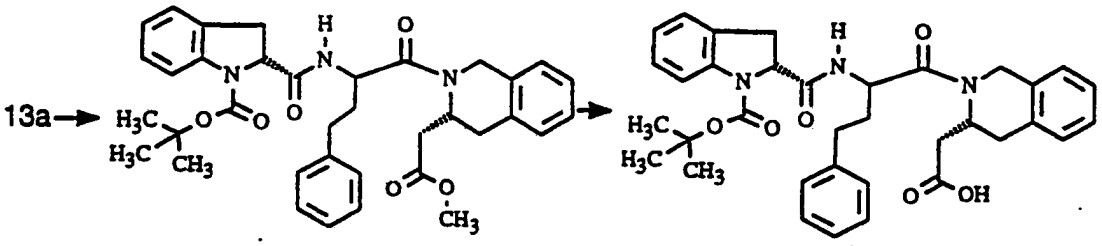
48b Methyl (3R)-2-{N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-O-benzyl-threonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **1d** on a 0.68 mmol scale following the method described for **32d** using **48a** instead of indole-3-acetic acid. The product was isolated in 82% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 35:65:1 v/v/v).
R_f (EtOAc:hexane:AcOH 50:50:1 v/v/v) 0.36

48c (3R)-2-{N-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-O-benzyl-threonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **48b** on a 0.56 mmol scale following the method descibed for **1f**. The product was isolated in 55% yield (195 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 50:50:1 v/v/v).
HPLC System A t_R=18.0' >98%
Mass spec (FAB) m/e=628 $[M+H]^+$

EXAMPLE 49



49a 49b

49a Methyl (3R)-2-{(2S)-2-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonylamino)-4-phenylbutanoyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **13a** on a 0.53 mmol scale following the method descibed for **48b**. The product was isolated in 80% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 30:70:2 v/v/v).

49b (3R)-2-{(2S)-2-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonylamino)-4-phenylbutanoyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

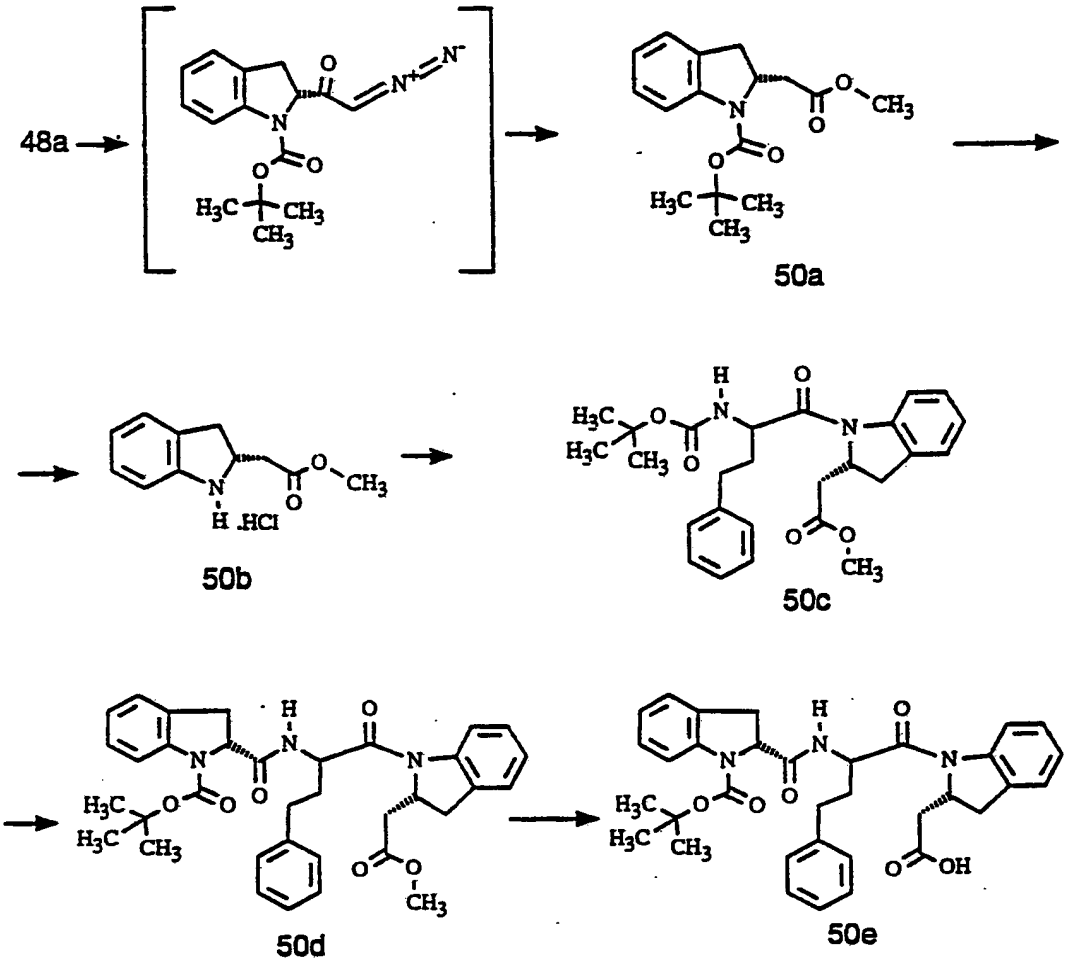
This was prepared from **49a** on a 0.21 mmol scale following the method descibed for **1f**. The product was isolated in 53% yield (66 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 35:65:2 v/v/v).

HPLC System A t_R=17.2' >98%

AAA Peptide content=85%

Mass spec (FAB) m/e=598 $[M+H]^+$

EXAMPLE 50



50a Methyl (2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-acetate.

This was prepared from **48a** on a 55 mmol scale following the method descibed for **1b**. The intermediate diazoketone was purified by flash chromatography on silica gel (eluant EtOAc:hexane 20:80 v/v), and the product was isolated in 69% yield after flash chromatography on silica gel (eluant EtOAc:hexane 12:88 v/v).

50b Methyl (2R)-2,3-dihydroindole-2-acetate hydrochloride.

This was prepared from **50a** on a 3 mmol scale following the method descibed for **1c** and was used without purification.

50c Methyl (2R)-1-{(2S)-2-*tert*-butyloxycarbonylamino-4-phenylbutanoyl}-2,3-dihydroindole-2-acetate.

This was prepared from **50b** on a 3 mmol scale following the method descibed for **1d** using BOC-homophenylalanine instead of N-BOC-O-benzyl-threonine. The product was isolated in 30% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 16:84 v/v).

50d Methyl (2R)-1-{(2S)-2-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetate.

This was prepared from **50c** on a 0.88 mmol scale following the method descibed for **48b**. The product was isolated in 89% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 30:70:2 v/v/v).

50e (2R)-1-{(2S)-2-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetic acid.

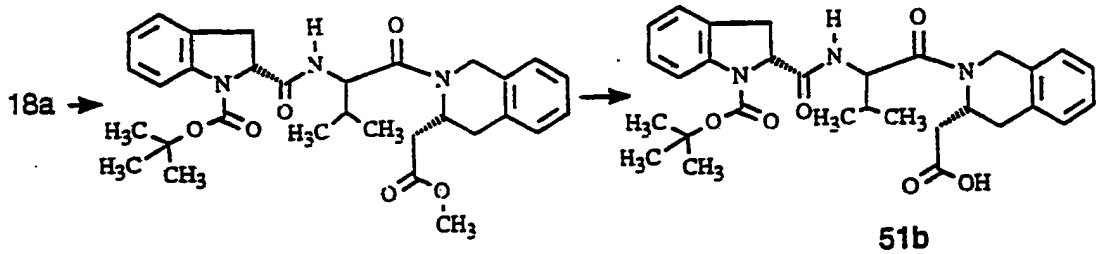
This was prepared from **50d** on a 0.16 mmol scale following the method descibed for **1f**. The product was isolated in 76% yield (70 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 45:55:2 v/v/v).

HPLC System B t_R=13.5' >95%

AAA Peptide content=92%

Mass spec (FAB) m/e=584 $[M+H]^+$

EXAMPLE 51



51a Methyl (3R)-2-{((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-valyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **18a** on a 0.41 mmol scale following the method descibed for **48b**. The product was isolated in 70% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v then neat EtOAc).

51b (3R)-2-{((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-valyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

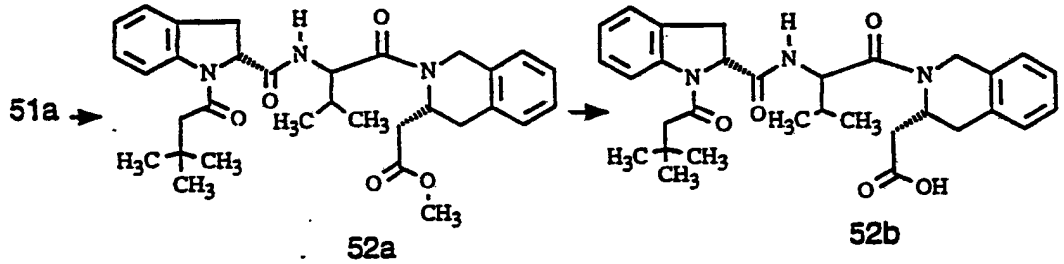
This was prepared from **51a** on a 0.29 mmol scale following the method descibed for **1f**. The product was isolated in 70% yield (108 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:1 v/v/v).

HPLC System B t_R=10.7' >98%

AAA Peptide content=81%

Mass spec (FAB) m/e=536 $[M+H]^+$

EXAMPLE 52



52a Methyl (3R)-2-{((2R)-1-*tert*-butylacetyl-2,3-dihydroindole-2-carbonyl)-valyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

A solution of **51a** (198 mg, 0.36 mmol) in 4*N* HCl in dioxan (15 mL) was stirred at room temperature for 30 min., then the solvent was evaporated *in vacuo*, finally with toluene azeotrope. The residue was taken up in CH_2Cl_2 and cooled to -15°C with stirring. Diisopropylethylamine (0.14 mL, 0.80 mmol) and *tert*-butylacetyl chloride (51 µL, 0.36 mmol) were added and the mixture was stirred at -15°C for 45 min. The solvent was evaporated *in vacuo*, and the residue was partitioned between EtOAc and 0.3*M* $KHSO_4$. The organic phase was washed with satd. $KHCO_3$, H_2O and brine, filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:hexane 55:45 v/v) to give the title compound (100 mg, 50%).

R_f (EtOAc:hexane 60:40 v/v) 0.28

52b (3R)-2-{((2R)-1-*tert*-Butylacetyl-2,3-dihydroindole-2-carbonyl)-valyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

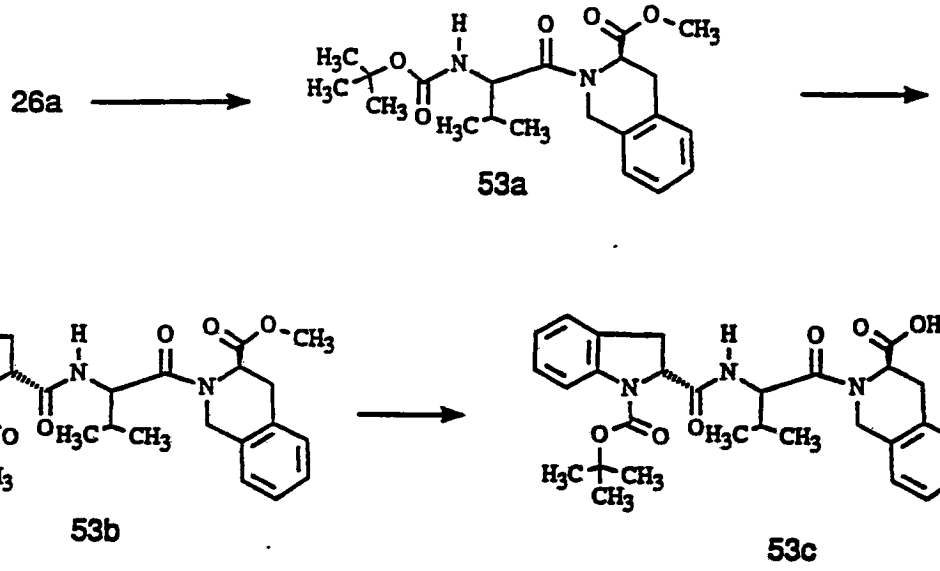
This was prepared from **52a** on a 0.18 mmol scale following the method descibed for **1f**. The product was isolated in 81% yield (78 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 65:35:1 v/v/v).

HPLC System A t_R=14.0' >98%

AAA Peptide content=76%

Mass spec (FAB) m/e=534 $[M+H]^+$

EXAMPLE 53



53a Methyl (3R)-2-(*tert*-butyloxycarbonyl-valyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from 26a on a 1.0 mmol scale following the method descibed for 1d using BOC-valine instead of N-BOC-O-benzyl-threonine. The product was isolated in 68% yield after flash chromatography on silica gel (eluant EtOAc:hexane 28:72 v/v).
R_f (EtOAc:hexane 25:75 v/v) 0.20

53b Methyl (3R)-2-{((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-valyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from 53a on a 0.68 mmol scale following the method descibed for 48b. The product was isolated in 81% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 45:55:1 v/v/v).
R_f (EtOAc:hexane:AcOH 50:50:1 v/v/v) 0.30

53c (3R)-2-{((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-valyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

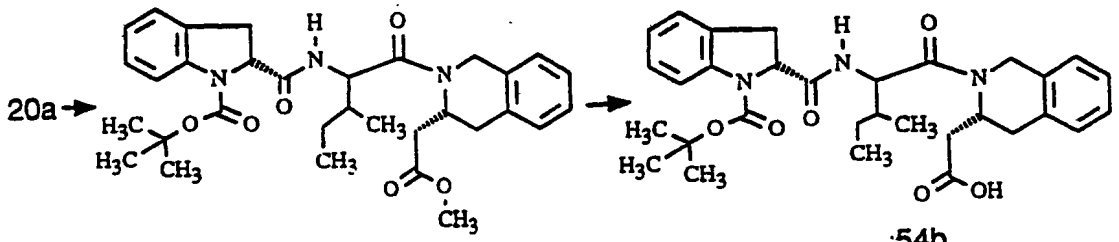
This was prepared from 53b on a 0.52 mmol scale following the method descibed for 1f. The product was isolated in 50% yield (150 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 60:40:1 v/v/v).

HPLC System A t_R=13.9' >98%

AAA Peptide content=77%

Mass spec (FAB) m/e=522 $[M+H]^+$

EXAMPLE 54



54a Methyl (3R)-2-{((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-isoleucyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **20a** on a 0.16 mmol scale following the method descibed for **48b**. The product was isolated in 94% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 35:65:2 v/v/v).

54b (3R)-2-{((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-isoleucyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

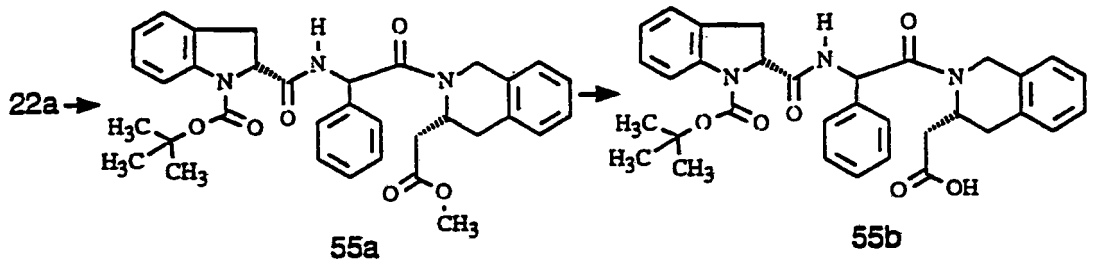
This was prepared from **54a** on a 0.15 mmol scale following the method descibed for **1f**. The product was isolated in 63% yield (55 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

HPLC System A t_R=15.3' >98%

AAA Peptide content=66%

Mass spec (FAB) m/e=550 $[M+H]^+$

EXAMPLE 55



55a Methyl (3R)-2-{(S)-α-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonylamino)-phenylacetyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **22a** on a 0.23 mmol scale following the method descibed for **48b.** The product was isolated in 89% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 35:65:2 v/v/v).

55b (3R)-2-{(S)-α-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonylamino)-phenylacetyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

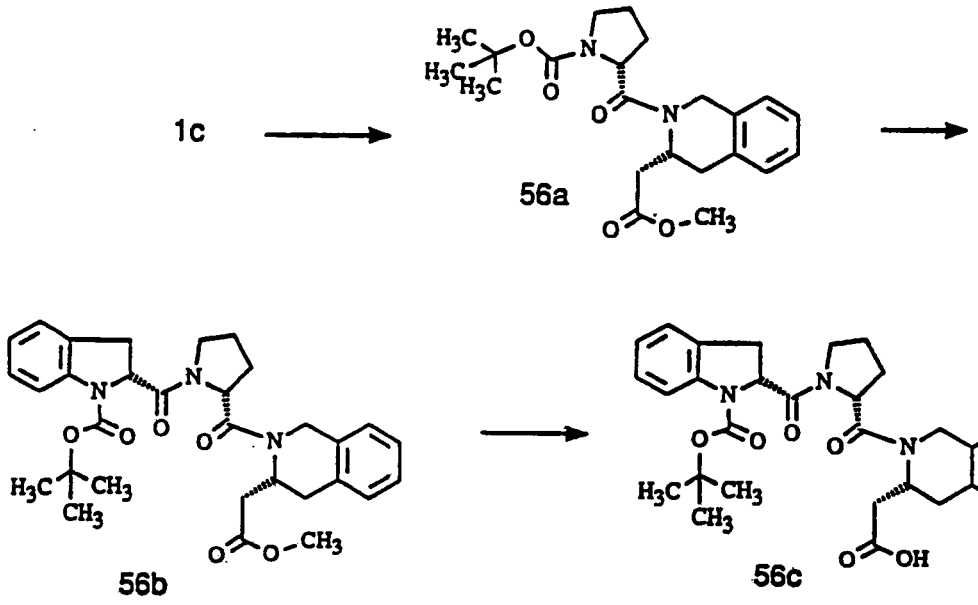
This was prepared from **55a** on a 0.21 mmol scale following the method descibed for **1f.** The product was isolated in 66% yield (87 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

HPLC System A t_R=15.3' >95%

AAA Peptide content=73%

Mass spec (FAB) m/e=570 $[M+H]^+$

EXAMPLE 56



56a Methyl (3R)-2-(*tert*-butyloxycarbonyl-D-prolyl)-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **1c** on a 1.0 mmol scale following the method descibed for **1d** using BOC-D-proline instead of N-BOC-O-benzyl-threonine. The product was isolated in 74% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 50:50 v/v).

56b Methyl (3R)-2-{((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-D-prolyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **56a** on a 0.37 mmol scale following the method descibed for **48b.** The product was isolated in 87% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 70:30:1 v/v/v).

56c (3R)-2-{((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-D-prolyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

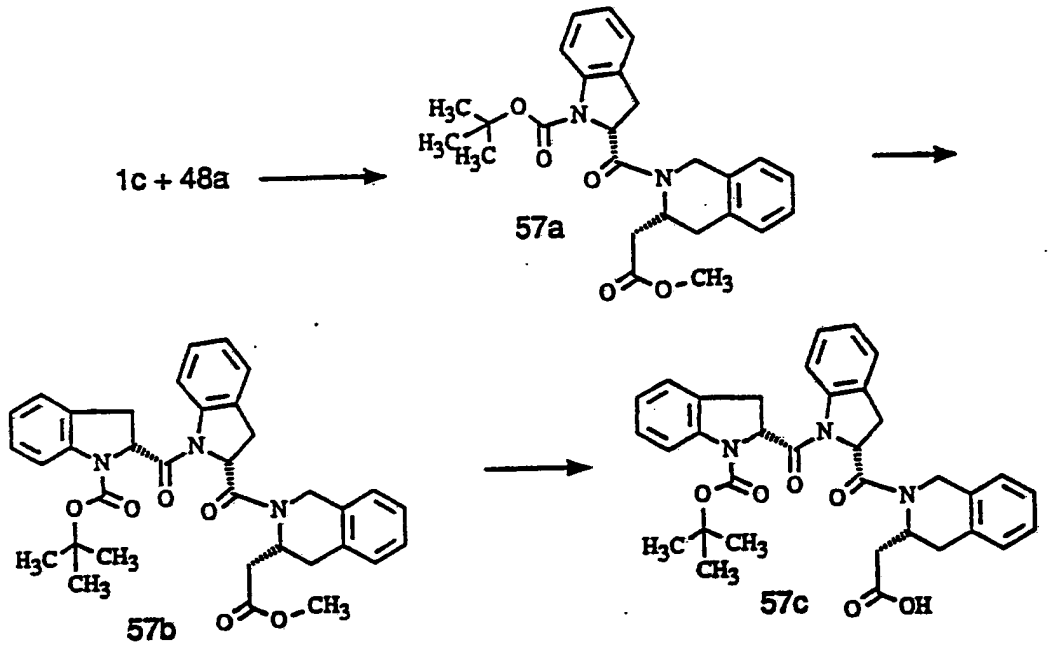
This was prepared from **56b** on a 0.32 mmol scale following the method descibed for **1f.** The product was isolated in 39% yield (67 mg) after flash chromatography on silica gel (eluant $CHCl_3$:MeOH:AcOH 50:2:1 v/v/v).

HPLC System B t_R=9.5' >98%

AAA Peptide content=73%

Mass spec (FAB) m/e=534 $[M+H]^+$

EXAMPLE 57



57a Methyl (3R)-2-{(2R)-1-(*tert*-butyloxycarbonyl)-2,3-dihydroindole-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **1c** on a 1.13 mmol scale following the method descibed for **1d** using **48a** instead of N-BOC-O-benzyl-threonine. The product was isolated in 79% yield after flash chromatography on silica gel (eluant EtOAc:hexane 30:70 v/v).

57b Methyl (3R)-2-{(2R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-2,3-dihydroindole-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **57a** on a 0.90 mmol scale following the method descibed for **48b**. The product was isolated in 64% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R_f (eluant EtOAc:hexane 60:40 v/v) 0.40

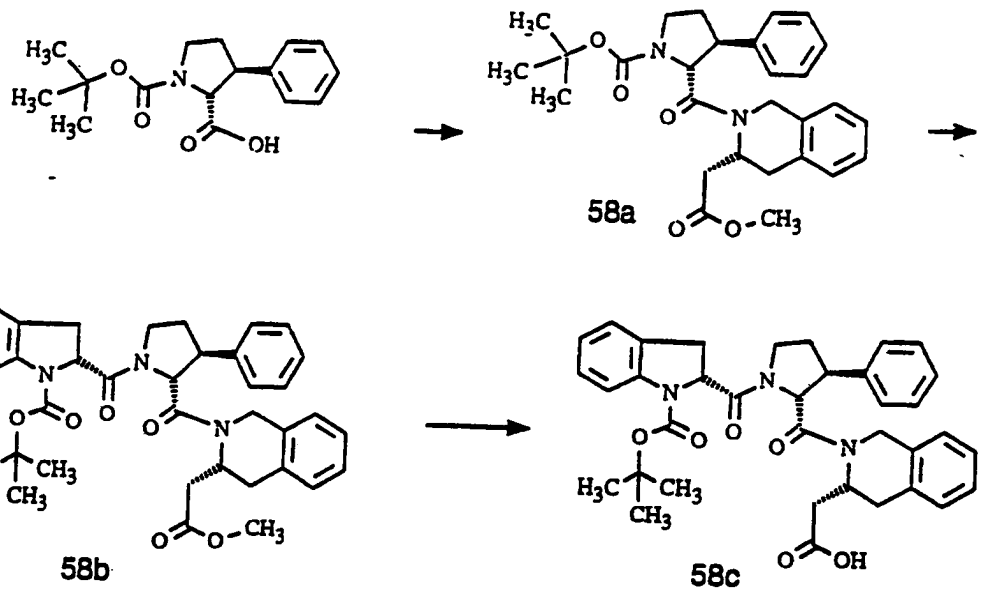
57c (3R)-2-{(2R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-2,3-dihydroindole-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **57b** on a 0.58 mmol scale following the method descibed for **1f**. The product was isolated in 65% yield (219 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 65:35:1 v/v/v).

HPLC System A t_R=17.7' >99%

Mass spec (FAB) m/e=582 $[M+H]^+$

EXAMPLE 58



58a Methyl (3R)-2-{(2R,3S)-1-*tert*-butyloxycarbonyl-3-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 1c on a 0.17 mmol scale following the method described for 1d using 1-*tert*-butyloxycarbonyl-3-phenyl-pyrrolidine-2-carboxylic acid (J.Y.L. Chung *et al*, *J.Org.Chem.*, 55.270,1990) instead of N-BOC-O-benzyl-threonine. The product was isolated in 75% yield and used without further purification.

R_f (EtOAc:pet. ether 50:50 v/v) 0.18

^{1}H NMR δ 1.28, 1.40, 1.48 (9H,3s); 3.59, 3.66 (3H,2s)

58b Methyl (3R)-2-{(2R,3S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-3-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 58a on a 0.098 mmol scale following the method described for 48b. The product was isolated in 78% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:1 v/v/v).

R_f (EtOAc:pet. ether:AcOH 60:40:1 v/v/v) 0.15

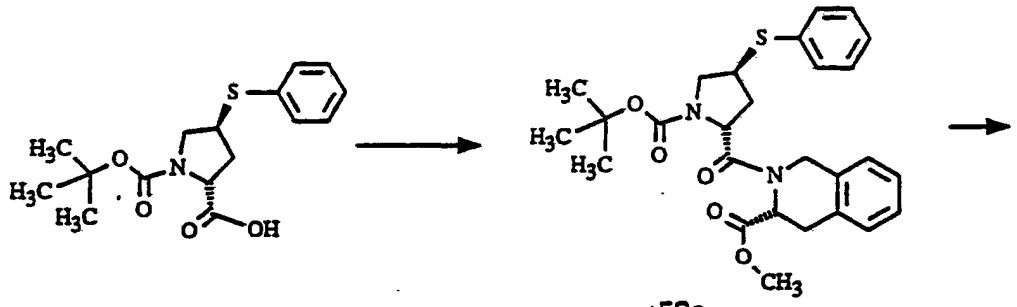
58c (3R)-2-{(2R,3S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-3-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **58b** on a 0.077 mmol scale following the method described for **1f**. The product was isolated in 83% yield (41 mg) without chromatography.

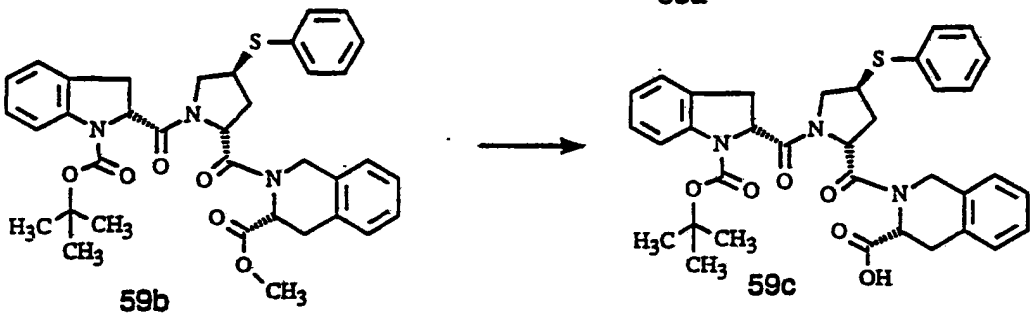
HPLC System B t_R=13.9' >99%

Mass spec (FAB) m/e=610 $[M+H]^+$

EXAMPLE 59



59a



59b **59c**

59a Methyl (3R)-2-{(2R,4S)-1-*tert*-butyloxycarbonyl-4-phenylthio-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **26a** on a 0.48 mmol scale following the method described for **1d** using (2R,4S)-1-*tert*-butyloxycarbonyl-4-phenylthio-pyrrolidine-2-carboxylic acid (J. Krapcho *et al, J.Med.Chem.*, 31,1148,1988) instead of N-BOC-O-benzyl-threonine. The product was isolated in 40% yield after flash chromatography on silica gel (eluant EtOAc:hexane 50:50 v/v).

R_f (EtOAc:hexane 60:40 v/v) 0.43

59b Methyl (3R)-2-{(2R,4S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenylthio-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **59a** on a 0.20 mmol scale following the method described for **48b**. The product was isolated in 61% yield after flash chromatography on silica gel (eluant EtOAc:hexane 50:50 v/v).

R_f (EtOAc:hexane 55:45 v/v) 0.42

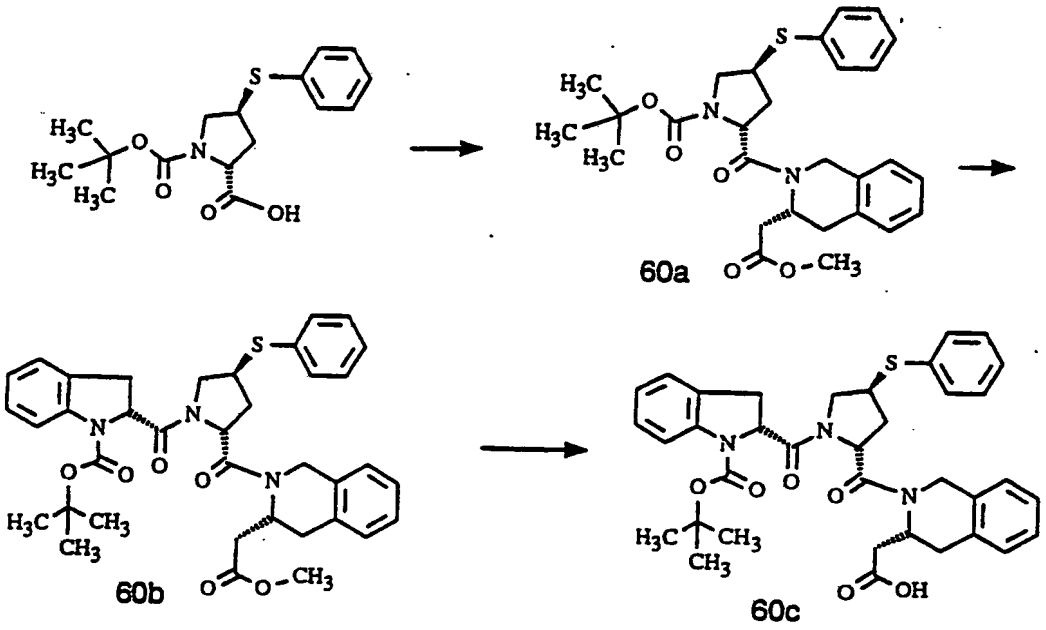
59c (3R)-2-{(2R,4S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenylthio-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **59b** on a 0.12 mmol scale following the method described for **1f**. The product was isolated in 43% yield (32 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 85:15:1 v/v).

HPLC System A t_R=20.5' >98%

Mass spec (FAB) m/e=627 $[M+H]^+$

EXAMPLE 60



60a Methyl (3R)-2-{(2R,4S)-1-*tert*-butyloxycarbonyl-4-phenylthio-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 1c on a 0.48 mmol scale following the method described for 1d using (2R,4S)-1-*tert*-butyloxycarbonyl-4-phenylthio-pyrrolidine-2-carboxylic acid instead of N-BOC-O-benzyl-threonine. The product was isolated in 61% yield after flash chromatography on silica gel (eluant EtOAc:hexane 50:50 v/v).

R_f (EtOAc:hexane 60:40 v/v) 0.39

60b Methyl (3R)-2-{(2R,4S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenylthio-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 60a on a 0.29 mmol scale following the method described for 48b. The product was isolated in 77% yield after flash chromatography on silica gel (eluant EtOAc:hexane 55:45 v/v).

R_f (EtOAc:hexane 60:40 v/v) 0.40

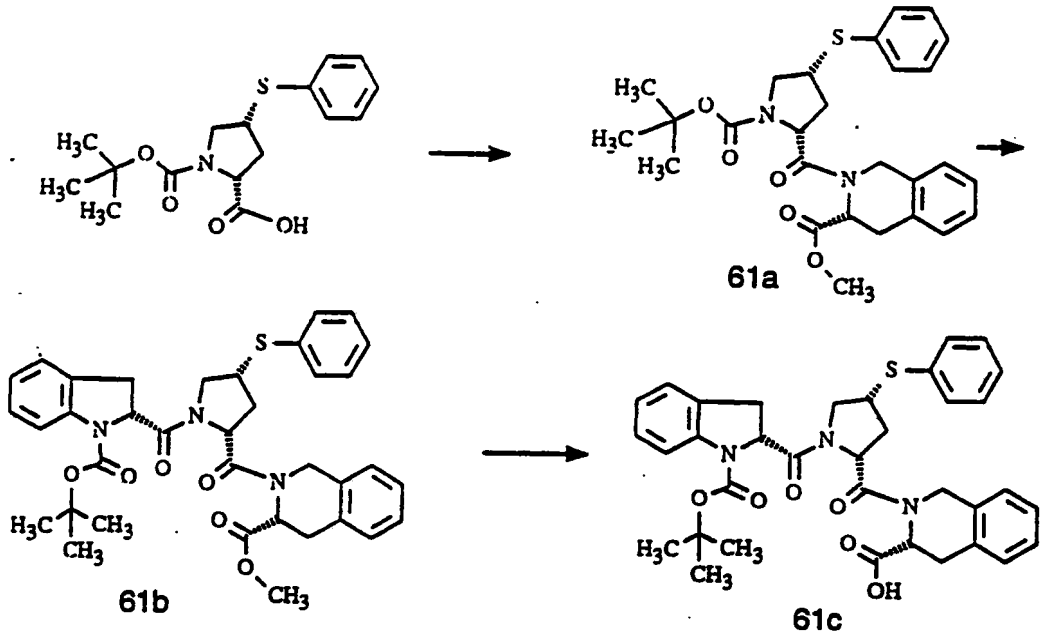
60c (3R)-2-{(2R,4S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenylthio-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 60b on a 0.22 mmol scale following the method described for 1f. The product was isolated in 64% yield (91 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 70:30:1 v/v).

HPLC System A t_R=20.9' >99%

Mass spec (FAB) m/e=642 $[M+H]^+$

EXAMPLE 61



61a Methyl (3R)-2-{(2R,4R)-1-*tert*-butyloxycarbonyl-4-phenylthio-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **26a** on a 0.40 mmol scale following the method described for **1d** using (2R,4R)-1-*tert*-butyloxycarbonyl-4-phenylthio-pyrrolidine-2-carboxylic acid (J. Krapcho *et al*, *J.Med.Chem.*, 31,1148,1988) instead of N-BOC-O-benzyl-threonine. The product was isolated in 60% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

61b Methyl (3R)-2-{(2R,4R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenylthio-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **61a** on a 0.24 mmol scale following the method described for **48b**. The product was isolated in 48% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

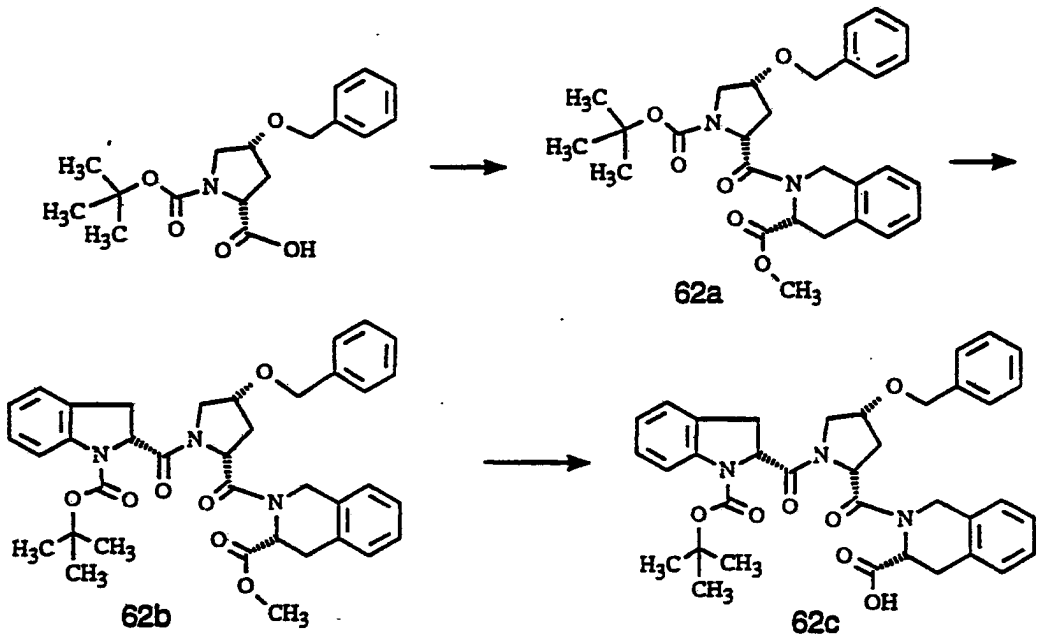
61c (3R)-2-{(2R,4R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenylthio-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **61b** on a 0.12 mmol scale following the method described for **1f**. The product was isolated in 69% yield (50 mg) after recrystallization from Et_2O/hexane.

HPLC System B t_R=15.0' >98%

Mass spec (FAB) m/e=628 $[M+H]^+$

EXAMPLE 62



62a Methyl (3R)-2-{(2R,4R)-1-*tert*-butyloxycarbonyl-4-benzyloxy-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **26a** on a 0.68 mmol scale following the method described for **1d** using (2R,4R)-1-*tert*-butyloxycarbonyl-4-benzyloxy-pyrrolidine-2-carboxylic acid (J. Krapcho *et al. J.Med.Chem.*, 31,1148,1988) instead of N-BOC-O-benzyl-threonine. The product was isolated in 43% yield after flash chromatography on silica gel (eluant EtOAc:hexane 50:50 v/v).

R_f (EtOAc:hexane 60:40 v/v) 0.38

62b. Methyl (3R)-2-{(2R,4R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-benzyloxy-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **62a** on a 0.30 mmol scale following the method described for **48b**. The product was isolated in 35% yield after flash chromatography on silica gel (eluant EtOAc:hexane 55:45 v/v).

R_f (EtOAc:hexane 60:40 v/v) 0.36

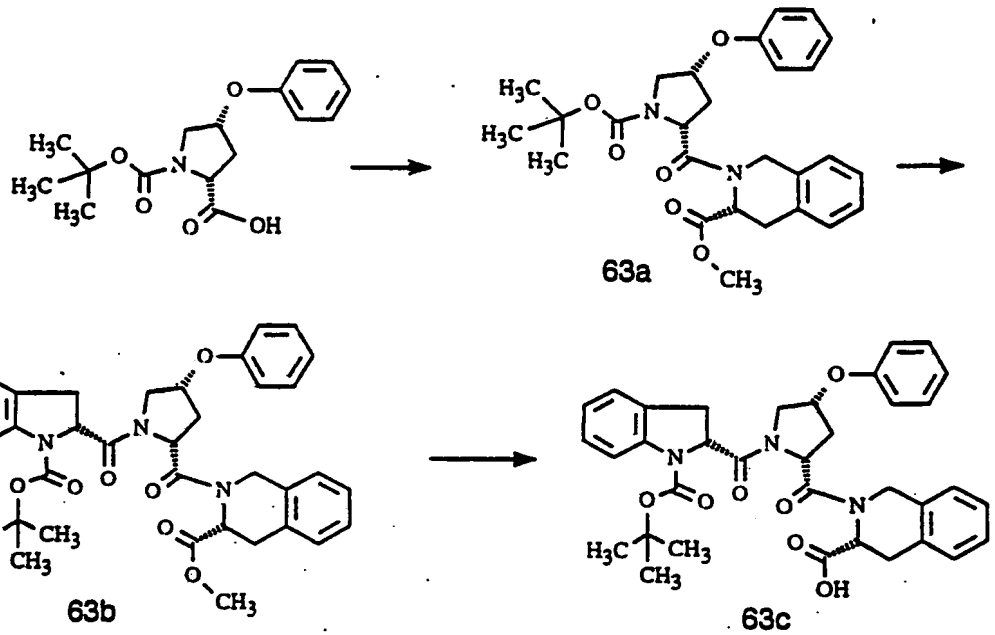
62c (3R)-2-{(2R,4R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-benzyloxy-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **62b** on a 0.11 mmol scale following the method described for **1f**. The product was isolated in 29% yield (20 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 90:10:1 v/v).

HPLC System A t_R=8.8' >98%

Mass spec (FAB) m/e=626 $[M+H]^+$

EXAMPLE 63



63a Methyl (3R)-2-{(2R.4R)-1-*tert*-butyloxycarbonyl-4-phenoxy-pyrrolidine-2-carbonyl}-1.2.3.4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **26a** on a 0.59 mmol scale following the method described for **1d** using (2R.4R)-1-*tert*-butyloxycarbonyl-4-phenoxy-pyrrolidine-2-carboxylic acid (J. Krapcho *et al. J.Med.Chem.*, 31.1148,1988) instead of N-BOC-O-benzyl-threonine. The product was isolated in 59% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

63b Methyl (3R)-2-{(2R.4R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenoxy-pyrrolidine-2-carbonyl}-1.2.3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **63a** on a 0.35 mmol scale following the method described for **48b.** The product was isolated in 20% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

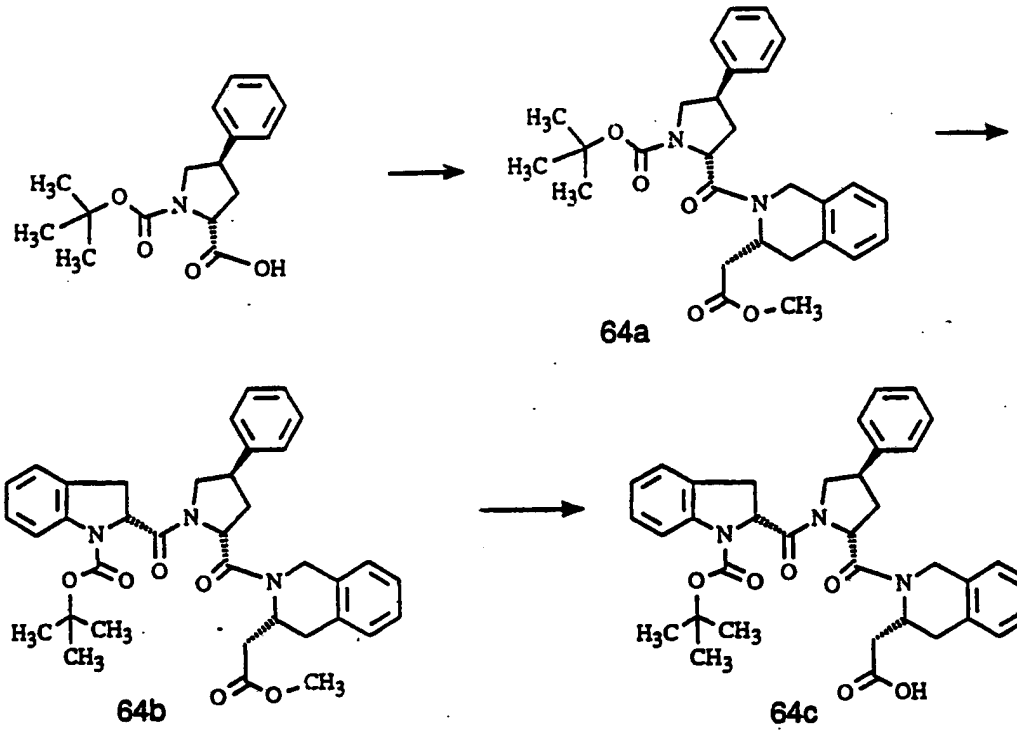
63c (3R)-2-{(2R,4R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenoxy-pyrrolidine-2-carbonyl}-1.2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **63b** on a 0.07 mmol scale following the method described for **1f.** The product was isolated in 61% yield (26 mg) after recrystallization from MeOH/H_2O.

HPLC System B t_R=13.2' >98%

Mass spec (FAB) m/e=612 $[M+H]^+$

EXAMPLE 64



64a Methyl (3R)-2-{(2R,4R)-1-*tert*-butyloxycarbonyl-4-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **1c** on a 0.24 mmol scale following the method described for **1d** using (2R,4S)-1-*tert*-butyloxycarbonyl-4-phenyl-pyrrolidine-2-carboxylic acid (J. Krapcho *et al*, *J.Med.Chem.*, 31,1148,1988) instead of N-BOC-O-benzyl-threonine. The product was used without further purification assuming a yield of 100%.

R_f (EtOAc:pet. ether 30:70 v/v) 0.11

64b Methyl (3R)-2-{(2R,4R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **64a** on a 0.24 mmol scale following the method described for **48b**. The product was isolated in 33% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:1 v/v/v).

R_f (EtOAc:pet. ether:AcOH 40:60:1) 0.09

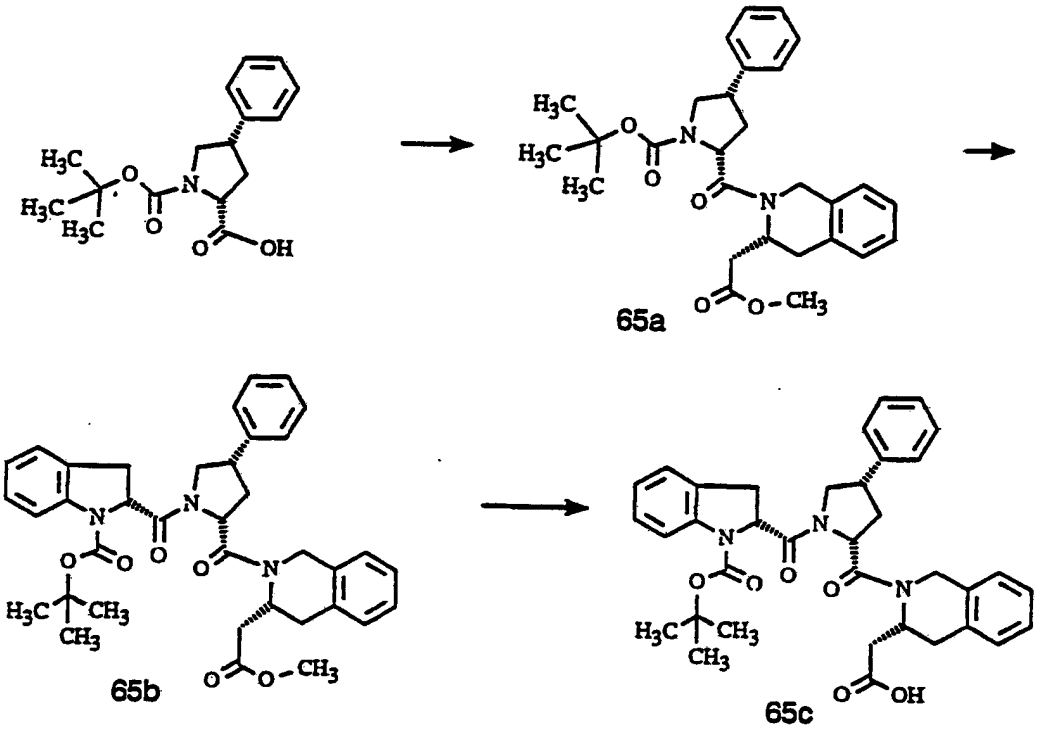
64c (3R)-2-{(2R,4R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **64b** on a 0.08 mmol scale following the method described for **1f**. The product was isolated in 100% yield (54 mg) without chromatography.

HPLC System B t_R=15.4' >98%

Mass spec (FAB) m/e=610 $[M+H]^+$

EXAMPLE 65



65a Methyl (3R)-2-{(2R,4S)-1-*tert*-butyloxycarbonyl-4-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **1c** on a 0.24 mmol scale following the method described for **1d** using (2R,4R)-1-*tert*-butyloxycarbonyl-4-phenyl-pyrrolidine-2-carboxylic acid (J. Krapcho *et al, J.Med.Chem.*, 31,1148,1988) instead of N-BOC-O-benzyl-threonine. The product was isolated in 78% yield and used without further purification.

R_f (EtOAc:pet. ether 30:70 v/v) 0.11

65b Methyl (3R)-2-{(2R,4S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **65a** on a 0.31 mmol scale following the method described for **48b**. The product was isolated in 74% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 30:70:1 v/v/v).

R_f (EtOAc:pet. ether:AcOH 25:85:1) 0.10

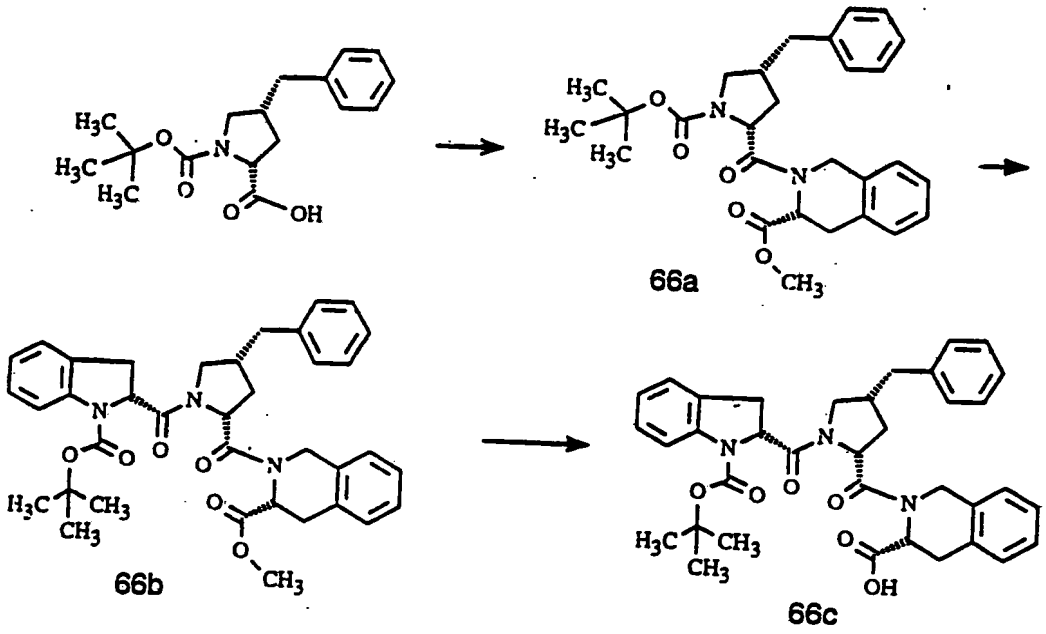
65c (3R)-2-{(2R,4S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **65b** on a 0.30 mmol scale following the method described for **1f**. The product was isolated in 79% yield (149 mg) without chromatography.

HPLC System B t_R=14.8' >95%

Mass spec (FAB) m/e=610 $[M+H]^+$

EXAMPLE 66



66a Methyl (3R)-2-{(2R,4S)-1-*tert*-butyloxycarbonyl-4-benzyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **26a** on a 0.66 mmol scale following the method described for 1d using (2R,4S)-1-*tert*-butyloxycarbonyl-4-benzyl-pyrrolidine-2-carboxylic acid (J. Krapcho *et al*, *J.Med.Chem.*, 31,1148,1988) instead of N-BOC-O-benzyl-threonine. The product was isolated in 55% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 30:70:1 v/v/v).

66b Methyl (3R)-2-{(2R,4S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-benzyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **66a** on a 0.35 mmol scale following the method described for **48b**. The product was isolated in 33% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 30:70:1 v/v/v).

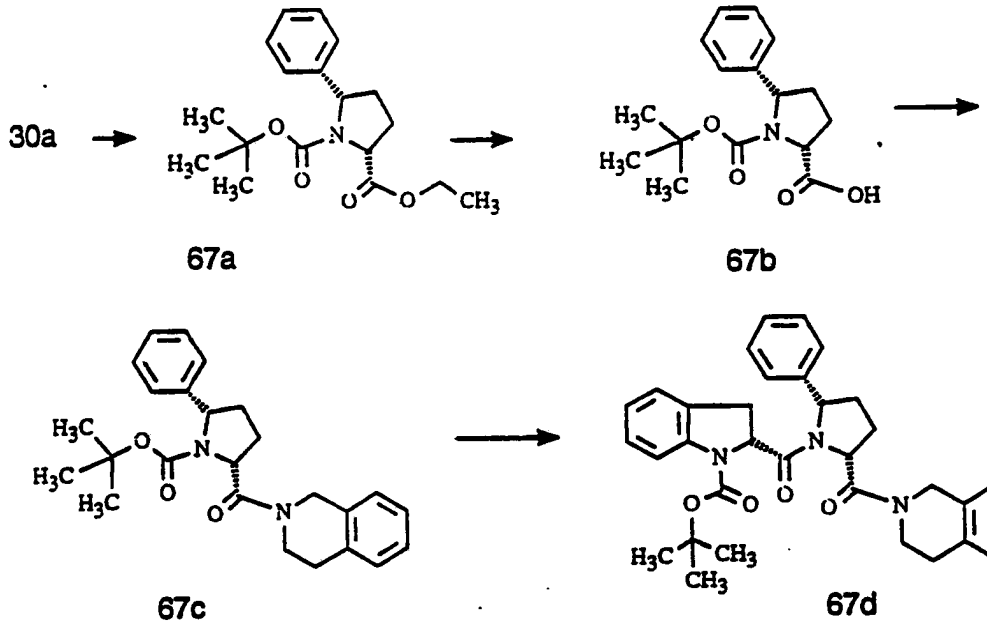
66c (3R)-2-{(2R,4S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-benzyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **66b** on a 0.11 mmol scale following the method described for **1f**. The product was isolated in 63% yield (43 mg) after recrystallization from MeOH/H_2O.

HPLC System B t_R=14.6' >95%

Mass spec (FAB) m/e=610 $[M+H]^+$

EXAMPLE 67



67a Ethyl (2R.5S)-1-*tert*-butyloxycarbonyl-5-phenyl-pyrrolidine-2-carboxylate.

To a solution of **30a** (290 mg, 1.32 mmol) in CH_2Cl_2 (10 mL) was added di-*tert*-butyl pyrocarbonate (576 mg, 2.64 mmol), and the mixture was stirred at room temperature for 3 hrs. The solvent was evaporated *in vacuo*, and the residue was purified by flash chromatography on silica gel (eluant EtOAc:pet. ether 15:85) to give the title compound (400 mg, 95%).

R_f (EtOAc:pet. ether 15:85) 0.35

67b (2R.5S)-1-*tert*-Butyloxycarbonyl-5-phenyl-pyrrolidine-2-carboxylic acid.

This was prepared from **67a** on a 1.25 mmol scale following the method described for **1f**. The product was isolated in 93% yield and used without further purification.

67c 2-{(2R.5S)-1-*tert*-Butyloxycarbonyl-5-phenyl-pyrrolidine-2-carbonyl}-1.2,3,4-tetrahydroisoquinoline.

This was prepared from **67b** and tetrahydroisoquinoline on a 0.38 mmol scale following the method described for **1d**. The product was isolated in 74% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

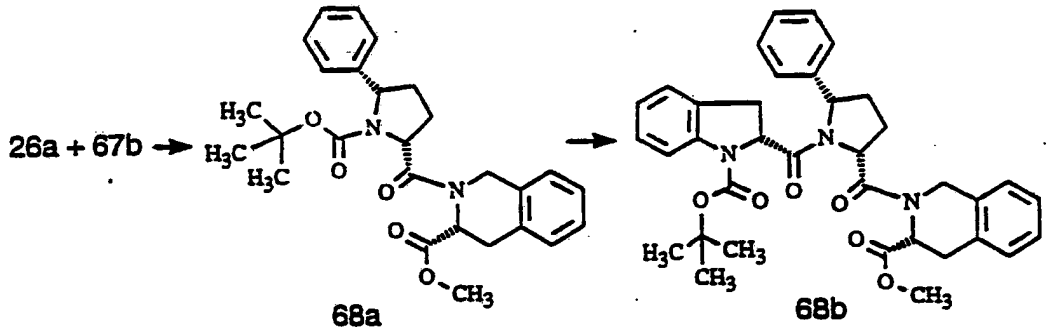
67d 2-{(2R.5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1.2.3.4-tetrahydroisoquinoline.

This was prepared from **67c** on a 0.28 mmol scale following the method described for **48b**. The product was isolated in 64% yield (98 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

HPLC System A t_R=25.0' >99%

Mass spec (FAB) m/e=552 $[M+H]^+$

EXAMPLE 68



68a Methyl (3R)-2-{(2R.5S)-1-*tert*-butyloxycarbonyl-5-phenyl-pyrrolidine-2-carbonyl}-1.2.3.4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **67b** and **26a** on a 0.27 mmol scale following the method described for **1d**. The product was isolated in 56% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

^{1}H NMR δ 1.13 (9H.s); 3.63 (3H.s); 5.69 (1H.t.J=4Hz)

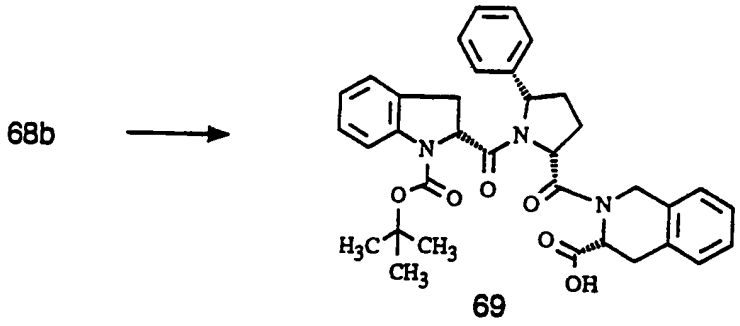
68b Methyl (3R)-2-{(2R.5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1.2.3.4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **68a** on a 1.0 mmol scale following the method described for **48b**. The product was isolated in 68% yield (415 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

HPLC System A t_R=24.7' >99%

Mass spec (FAB) m/e=610 $[M+H]^+$

EXAMPLE 69



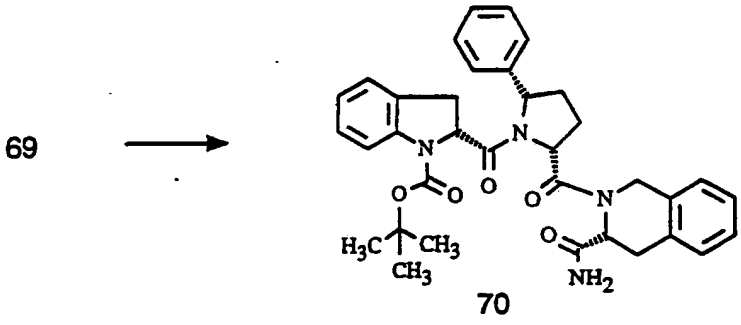
69 (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **68b** on a 0.13 mmol scale following the method described for **1f**. The product was isolated in 50% yield (38 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:2 v/v/v).

HPLC System A t_R=14.9' >98%

Mass spec (FAB) m/e=618 $[M+Na]^+$

EXAMPLE 70



70 (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide.

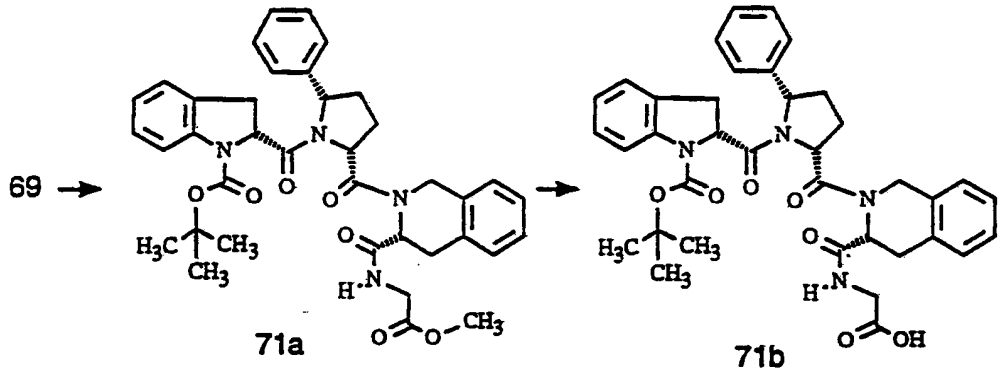
To an ice-cold stirred solution of **69** (107 mg, 0.18 mmol) and pentafluorophenol (37 mg, 0.2 mmol) in CH_2Cl_2 (10 mL) was added WSCD.HCl (478 mg, 0.4 mmol). The mixture was stirred at 0°C for 1 hr., then c. aqueous NH_3 (0.5 mL) was added and vigorous stirring was continued for 3 hr. The mixture was partitioned between EtOAc and H_2O, and the organic phase was washed with 10% $KHSO_4$, satd. $KHCO_3$ and brine, filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo*. The residue was

purified by flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 55:45:2 v/v/v) to give the title compound (87 mg, 81%).

HPLC System A t_R=20.1' >99%

Mass spec (FAB) m/e=595 $[M+H]^+$

EXAMPLE 71



71a Methyl N-{(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carbonyl}-glycinate.

This was prepared from **69** on a 0.30 mmol scale following the method described for **38b**. The product was isolated in 85% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 65:35 v/v).

71b N-{(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carbonyl}-glycine.

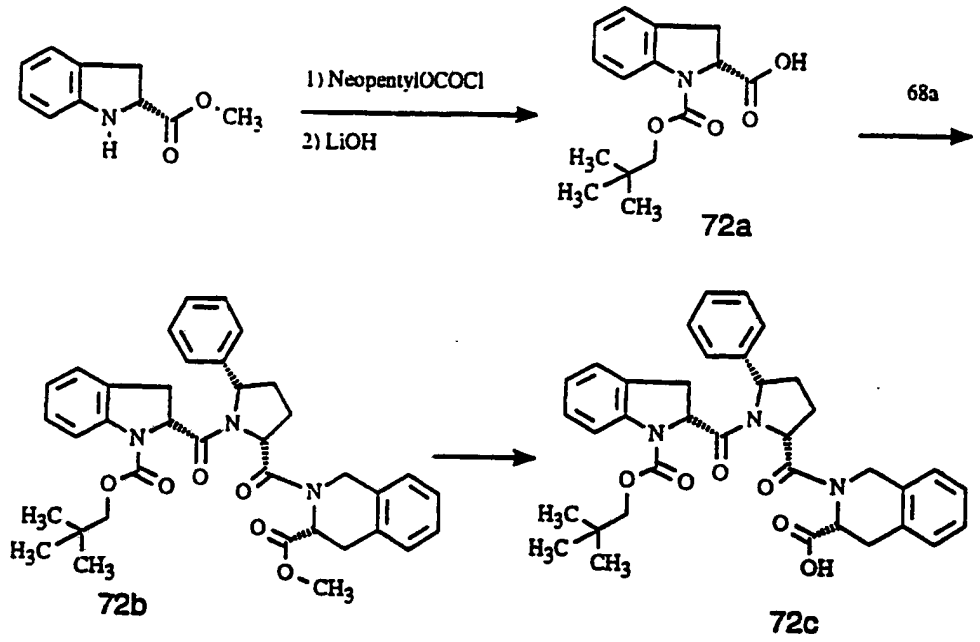
This was prepared from **71a** on a 0.26 mmol scale following the method described for **1f**. The product was isolated in 71% yield (120 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System A t_R=18.4' >99%

AAA Peptide content=76%

Mass spec (FAB) m/e=653 $[M+H]^+$

EXAMPLE 72



72a (2R)-1-Neopentyloxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

To an ice-cold stirred solution of neopentyl alcohol (88mg, 1 mmol) in CH_2Cl_2 (5 mL) was added triphosgene (110 mg, 0.37 mmol) and pyridine (84 µL, 1.02 mmol). The mixture was allowed to warm to room temperature and stirred for 1 hr. then cooled to 0°C. A solution of methyl (2R)-2,3-dihydroindole-2-carboxylate hydrochloride (107 mg, 0.5 mmol) and diisopropylethylamine (90 µL, 0.45 mmol) in CH_2Cl_2 (2 mL) was added and the mixture was stirred at room temperature for 3 hr. The solvent was removed *in vacuo* and the residue was taken up in EtOAc. The solution was washed with 1*M* HCl (x3) and brine, filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo*. The residue was taken up in dioxan (10 mL) and a solution of LiOH (24 mg, 1 mmol) in H_2O (2 mL) was added. The mixture was stirred at room temperature for 90 min., then the solvent was evaporated *in vacuo* and the residue was partitioned between EtOAc and 10% aq. $KHSO_4$. The organic phase was washed with brine, filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo* to give the title compound (90 mg, 62%) which was used without further purification.

72b Methyl (3R)-2-{(2R,5S)-1-((2R)-1-neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **68a** and **72a** on a 0.29 mmol scale following the method described for **48b**. The product was isolated in 50% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

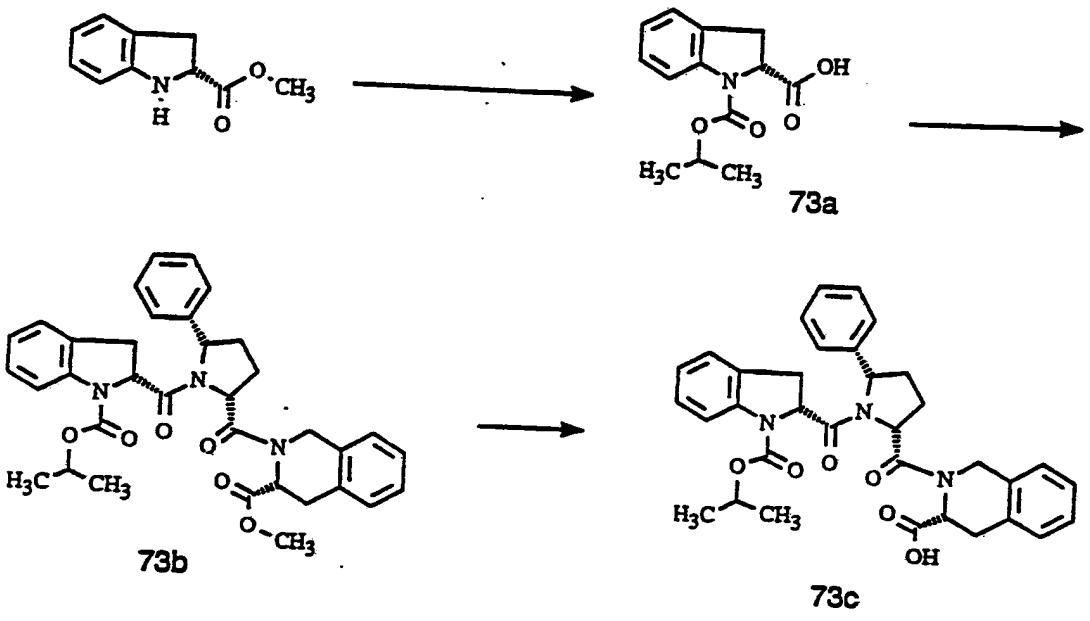
72c (3R)-2-{(2R,5S)-1-((2R)-1-Neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **72b** on a 0.14 mmol scale following the method described for **1f**. The product was isolated in 81% yield (69 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:2 v/v/v).

HPLC System A t_R=22.4' >95%

Mass spec (FAB) m/e=610 $[M+H]^+$

EXAMPLE 73



73a (2R)-1-Isopropyloxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from isopropanol on a 0.5 mmol scale following the method described for **72a**. The product was isolated in 80% yield and used without further purification.

73b Methyl (3R)-2-{(2R,5S)-1-((2R)-1-isopropyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **68a** and **73a** on a 0.33 mmol scale following the method described for **48b**. The product was isolated in 59% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 45:55 v/v).

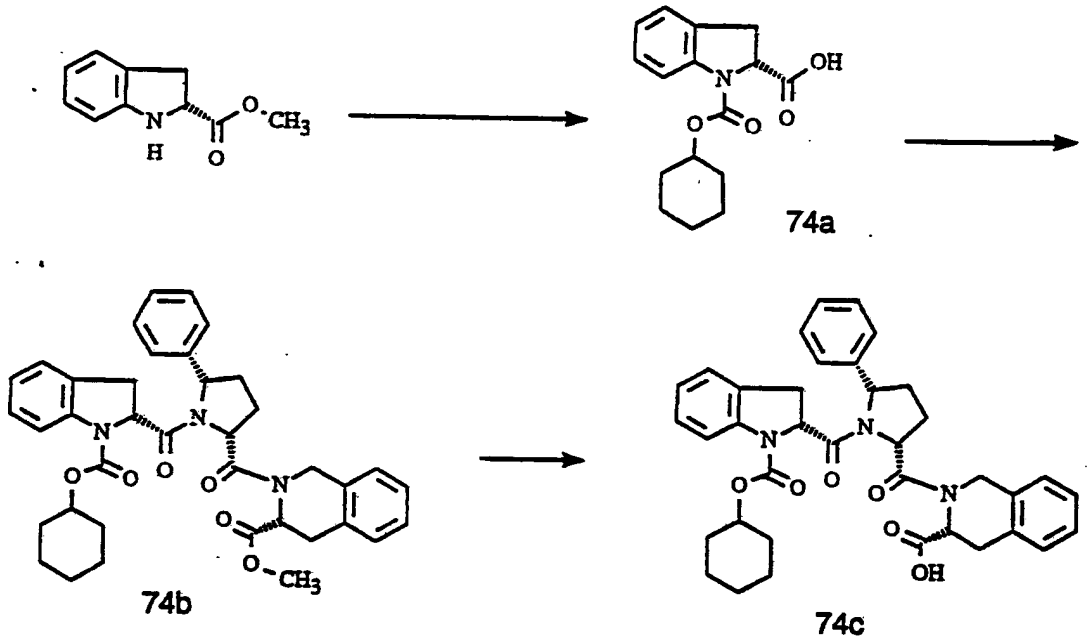
73c (3R)-2-{(2R,5S)-1-((2R)-1-Isopropyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **73b** on a 0.19 mmol scale following the method described for **1f**. The product was isolated in 63% yield (70 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:2 v/v/v).

HPLC System A t_R=18.5' >90%

Mass spec (FAB) m/e=582 $[M+H]^+$

EXAMPLE 74



74a (2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from cyclohexanol on a 0.5 mmol scale following the method described for **72a**. The product was isolated in 72% yield and used without further purification.

74b Methyl (3R)-2-{(2R,5S)-1-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

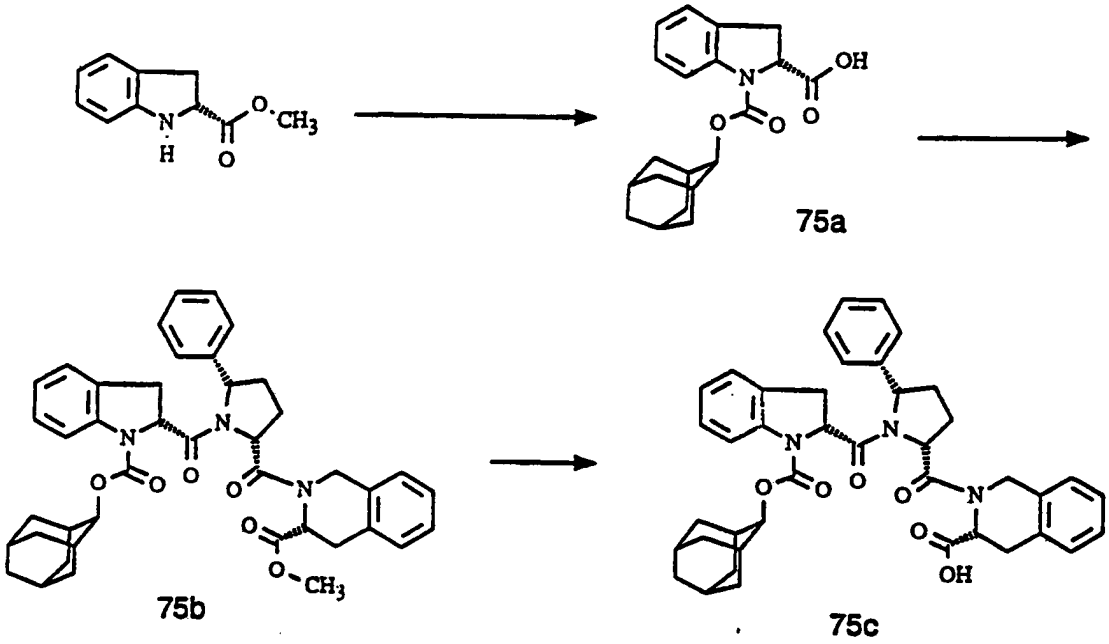
This was prepared from **68a** and **74a** on a 0.27 mmol scale following the method described for **48b**. The product was isolated in 73% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

74c (3R)-2-{(2R,5S)-1-((2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **74b** on a 0.20 mmol scale following the method described for **1f**. The product was isolated in 84% yield (104 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 55:45:2 v/v/v).

HPLC System A t_R=23.0' >95%
Mass spec (FAB) m/e=621 $[M+H]^+$

EXAMPLE 75



75a (2R)-1-(2-Adamantyl)oxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from 2-adamantanol on a 0.5 mmol scale following the method described for **72a**. The product was isolated in 80% yield and used without further purification.

75b Methyl (3R)-2-{(2R,5S)-1-((2R)-1-(2-adamantyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **68a** and **75a** on a 0.33 mmol scale following the method described for **48b**. The product was isolated in 29% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

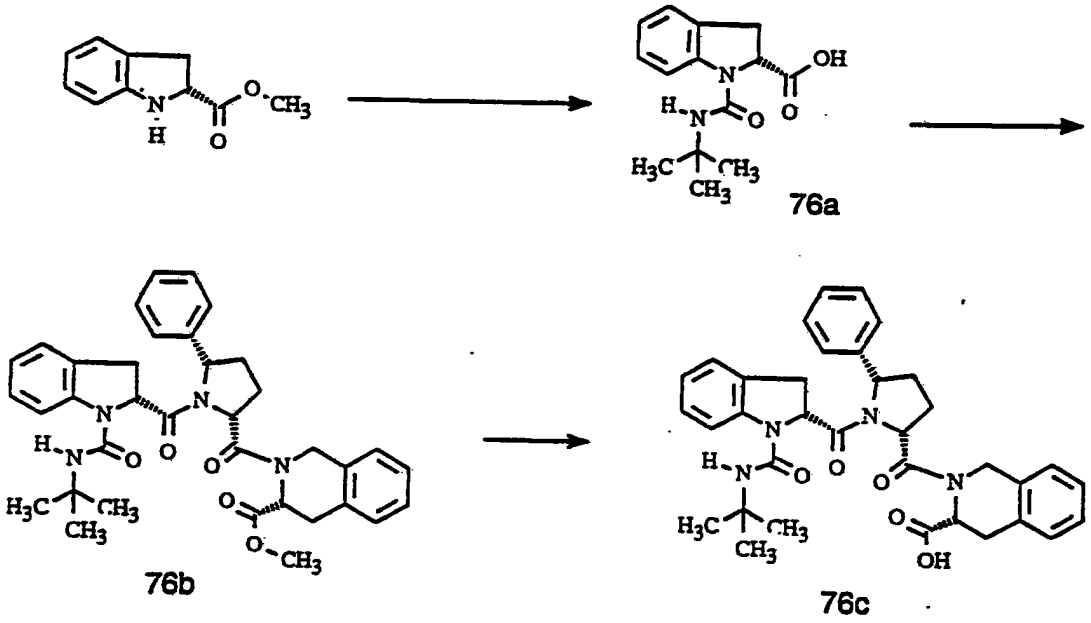
75c (3R)-2-{(2R,5S)-1-((2R)-1-(2-Adamantyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **75b** on a 0.09 mmol scale following the method described for 1f. The product was isolated in 81% yield (49 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 55:45:2 v/v/v).

HPLC System A t_R=27.9' >98%

Mass spec (FAB) m/e=674 $[M+H]^+$

EXAMPLE 76



76a (2R)-1-*tert*-Butylcarbamoyl-2,3-dihydroindole-2-carboxylic acid.

To an ice-cold stirred solution of methyl (2R)-2,3-dihydroindole-2-carboxylate hydrochloride (107 mg, 0.5 mmol) and diisopropylethylamine (110 µL, 0.6 mmol) in CH_2Cl_2 (2 mL) was added tert-butylisocyanate (120 mg, 1.2 mmol). The mixture was allowed to warm to room temperature and stirred for 6 days then the solvent was removed *in vacuo* and the residue was taken up in EtOAc. The solution was washed with 1*M* HCl (x3) and brine, filtered (Whatman^R IPS phase separator), and concentrated *in vacuo*. The residue was taken up in dioxan (10 mL) and a solution of LiOH (24 mg, 1 mmol) in H_2O

(2 mL) was added. The mixture was stirred at room temperature for 90 min., then the solvent was evaporated *in vacuo* and the residue was partitioned between EtOAc and 10% aq. $KHSO_4$. The organic phase was washed with brine, filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo* to give the title compound (120 mg, 91%) which was used without further purification.

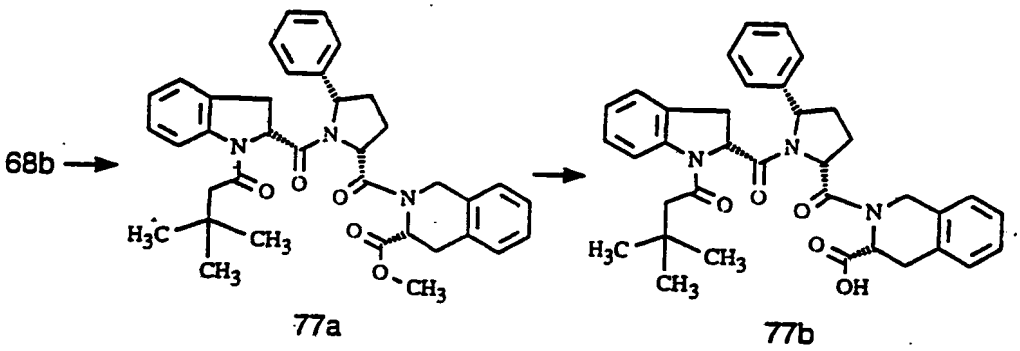
76b Methyl (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-butylcarbamoyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **68a** and **76a** on a 0.37 mmol scale following the method described for **48b**. The product was isolated in 13% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 50:50 v/v).

76c (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butylcarbamoyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **76b** on a 0.05 mmol scale following the method described for **1f**. The product was isolated in 67% yield (20 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 75:25:2 v/v/v).
HPLC System A t_R=12.2' >98%
Mass spec (FAB) m/e=595 $[M+H]^+$

EXAMPLE 77



77a Methyl (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-butylacetyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **68b** on a 0.18 mmol scale following the method described for **52a**. The product was isolated in 81% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

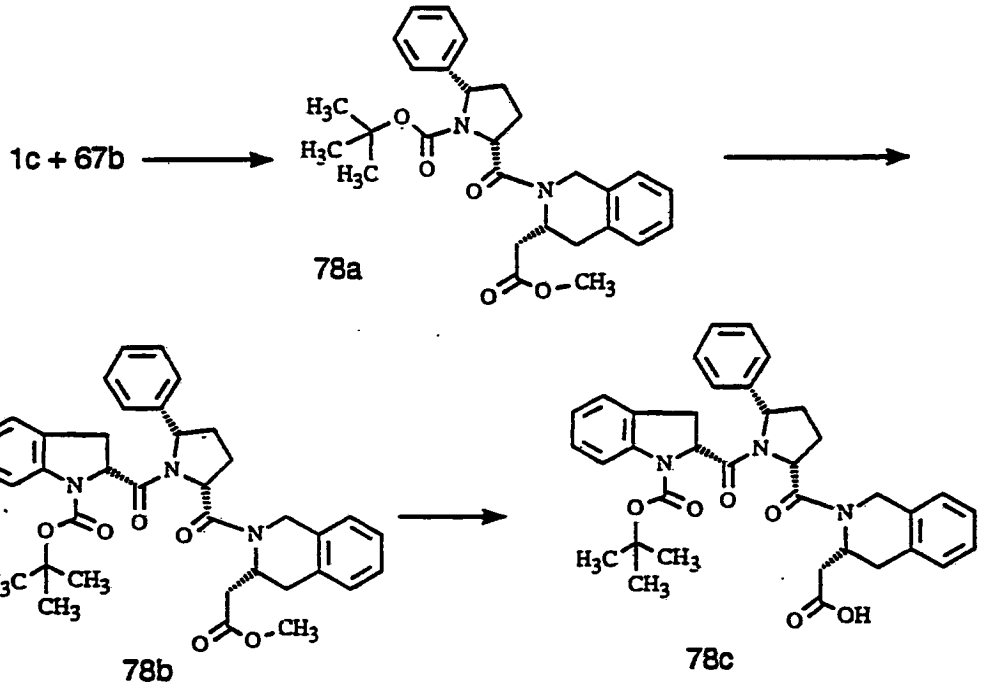
77b (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butylacetyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **77a** on a 0.14 mmol scale following the method described for **1f**. The product was isolated in 82% yield (68 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:2 v/v/v).

HPLC System A t_R=20.0' >99%

Mass spec (FAB) m/e=594 $[M+H]^+$

EXAMPLE 78



78a Methyl (3R)-2-{(2R.5S)-1-*tert*-butyloxycarbonyl-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 1c and **67b** on a 0.58 mmol scale following the method described for **1d.** The product was isolated in 87% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

78b Methyl (3R)-2-{(2R.5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **78a** on a 0.36 mmol scale following the method described for **48b.** The product was isolated in 98% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

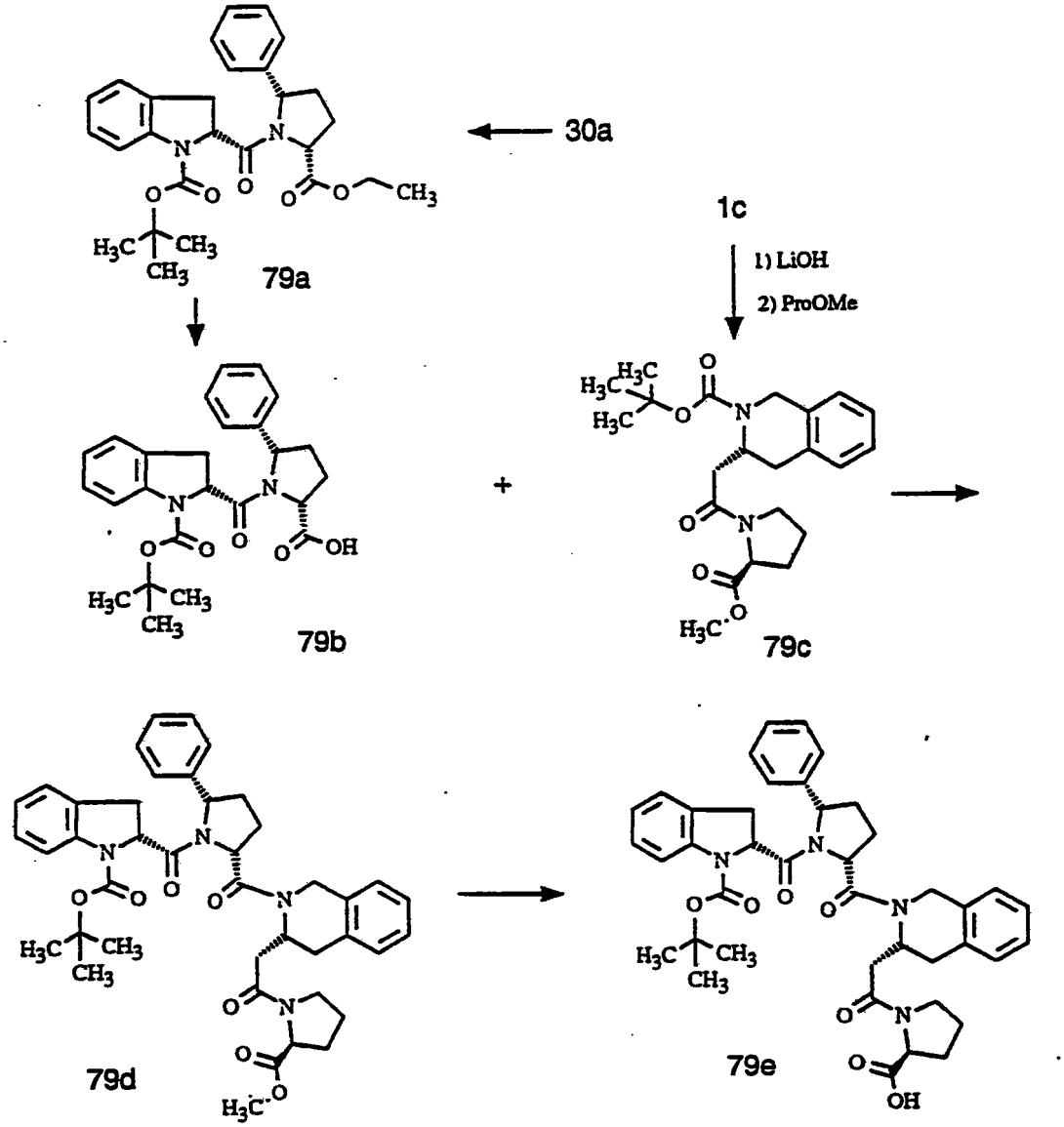
78c (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **78b** on a 0.35 mmol scale following the method described for **1f.** The product was isolated in 45% yield (95 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:3 v/v/v).

HPLC System A t_R=15.7' >99%

Mass spec (FAB) m/e=610 $[M+H]^+$

EXAMPLE 79



79a Ethyl (2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carboxylate.

This was prepared from **30a** on a 1.37 mmol scale following the method described for **48b**. The product was isolated in 86% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

R_f (EtOAc:hexane 40:60 v/v) 0.29

79b (2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carboxylic acid.

This was prepared from **79a** on a 1.18 mmol scale following the method described for **1f**. The product was isolated in 66% yield and used without further purification.

R_f (EtOAc:hexane:AcOH 80:20:2 v/v/v) 0.31

79c Methyl N-{(3R)-2-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-acetyl}-prolinate.

This was prepared from **1b** on a 1.25 mmol scale in two steps. **1b** was hydrolysed following the method described for **1f**, and the crude acid was coupled to ProOMe following the method described for **1d**. The product was isolated in 86% yield after flash chromatography on silica gel (eluant EtOAc:hexane 60:40 v/v).

R_f (EtOAc:hexane 60:40 v/v) 0.23

79d Methyl N-{(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetyl}-prolinate.

This was prepared from **79c** on a 0.14 mmol scale in two steps. **79c** was deprotected following the method described for **1c**, and the crude amine was coupled to **79b** following the method described for **1d**. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 80:20 v/v).

R_f (EtOAc:hexane 80:20 v/v) 0.19

79e N-{(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetyl}-proline.

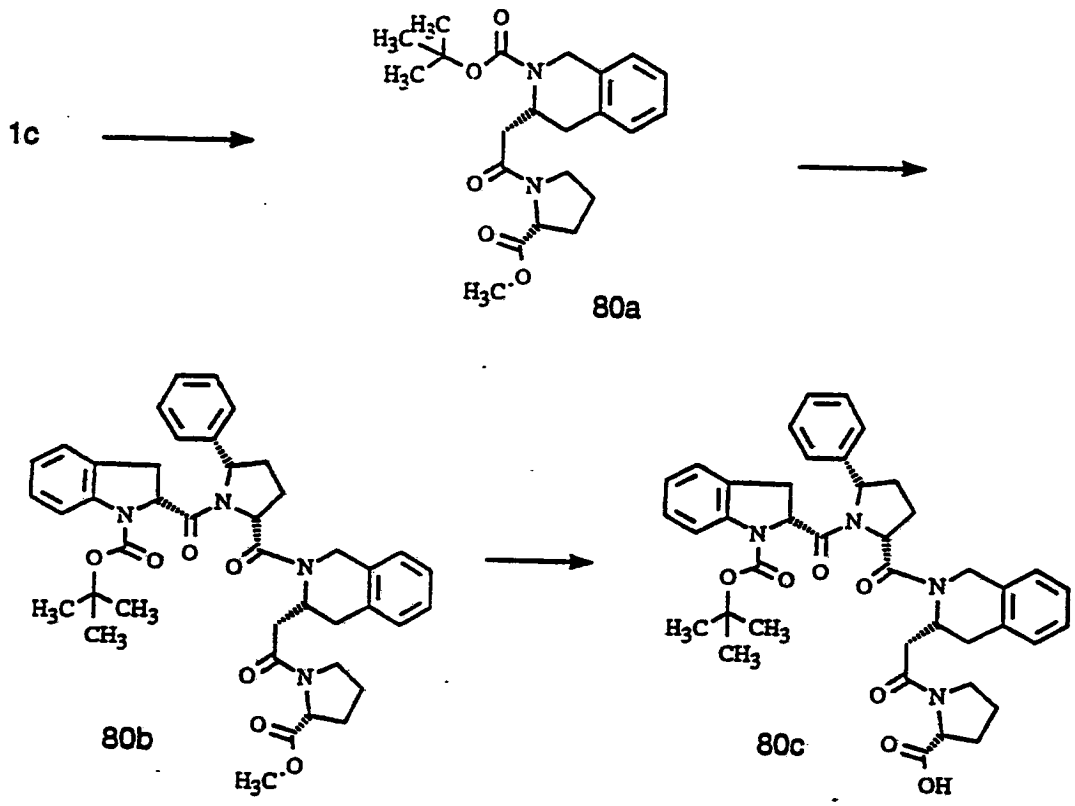
This was prepared from **79d** on a 0.14 mmol scale following the method described for **1f**. The product was isolated in 45% yield (45 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System A t_R=18.5' >98%

AAA Peptide content=91%

Mass spec (FAB) m/e=707 $[M+H]^+$

EXAMPLE 80



80a Methyl N-{(3R)-2-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-acetyl}-D-prolinate.

This was prepared from **1b** on a 1.25 mmol scale following the method described for **79c** using D-ProOMe. The product was isolated in 43% yield after flash chromatography on silica gel (eluant EtOAc:hexane 70:30 v/v).

R_f (EtOAc:hexane 60:40 v/v) 0.27

80b Methyl N-{(3R)-2-{(2R.5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1.2.3,4-tetrahydroisoquinoline-3-acetyl}-D-prolinate.

This was prepared from **80a** on a 0.13 mmol scale following the method described for **79d**. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 80:20 v/v).

R_f (EtOAc:hexane 80:20 v/v) 0.18

80c N-{(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetyl}-D-proline.

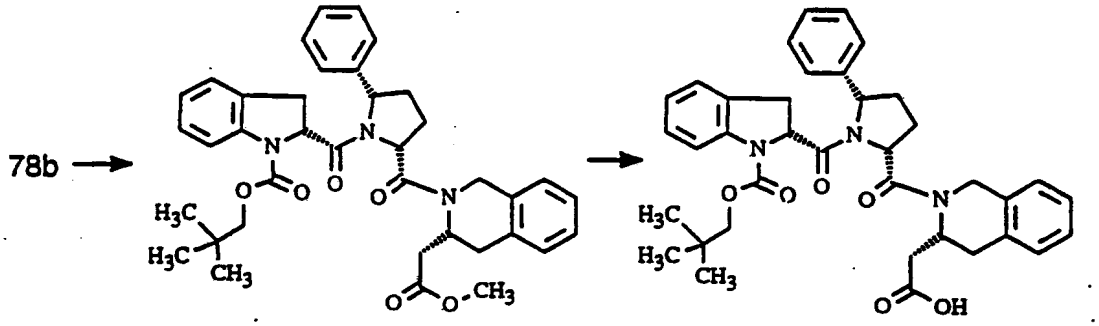
This was prepared from **80b** on a 0.13 mmol scale following the method described for **1f**. The product was isolated in 50% yield (49 mg) after flash chromatography on silica gel (eluant $CHCl_3$:MeOH:AcOH 50:2:1 v/v/v).

HPLC System A t_R=17.8' >98%

AAA Peptide content=91%

Mass spec (FAB) m/e=707 $[M+H]^+$

EXAMPLE 81



81a Methyl (3R)-2-{(2R.5S)-1-((2R)-1-neopentyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **78b** on a 0.27 mmol scale in two steps. **78b** was deprotected following the method described for **1c**, and the crude amine was reacted with neopentyl chloroformate following the method described for **72a** (excluding the final hydrolysis).

The product was isolated in 70% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

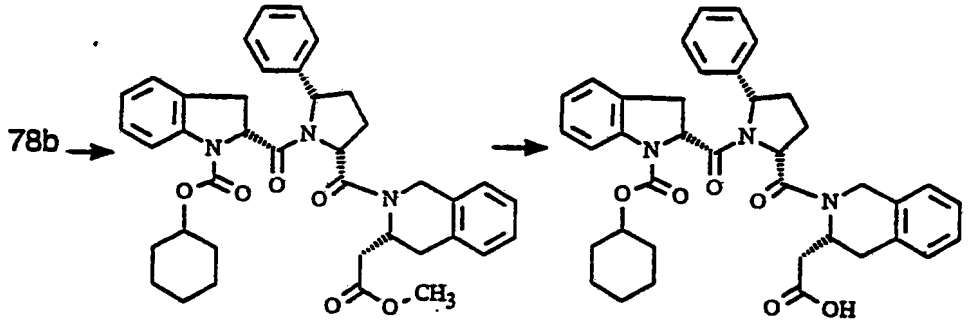
81b (3R)-2-{(2R,5S)-1-((2R)-1-Neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **81a** on a 0.19 mmol scale following the method described for **1f**. The product was isolated in 70% yield (82 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).

HPLC System B t_R=17.5' >95%

Mass spec (FAB) m/e=624 $[M+H]^+$

EXAMPLE 82



82a Methyl (3R)-2-{(2R,5S)-1-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

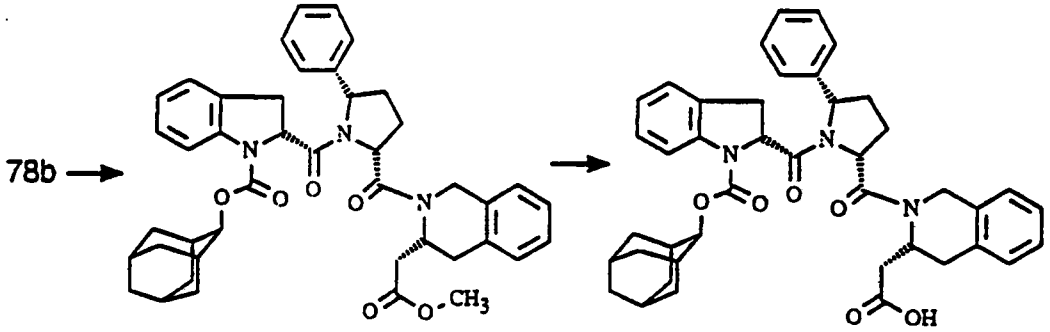
This was prepared from **78b** on a 0.27 mmol scale following the method described for **81a** using cyclohexanol instead of neopentyl alcohol. The product was isolated in 62% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).

82b (3R)-2-{(2R,5S)-1-((2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **82a** on a 0.17 mmol scale following the method described for **1f**. The product was isolated in 82% yield (86 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).

HPLC System B t_R=18.1' >98%
Mass spec (FAB) m/e=636 $[M+H]^+$

EXAMPLE 83



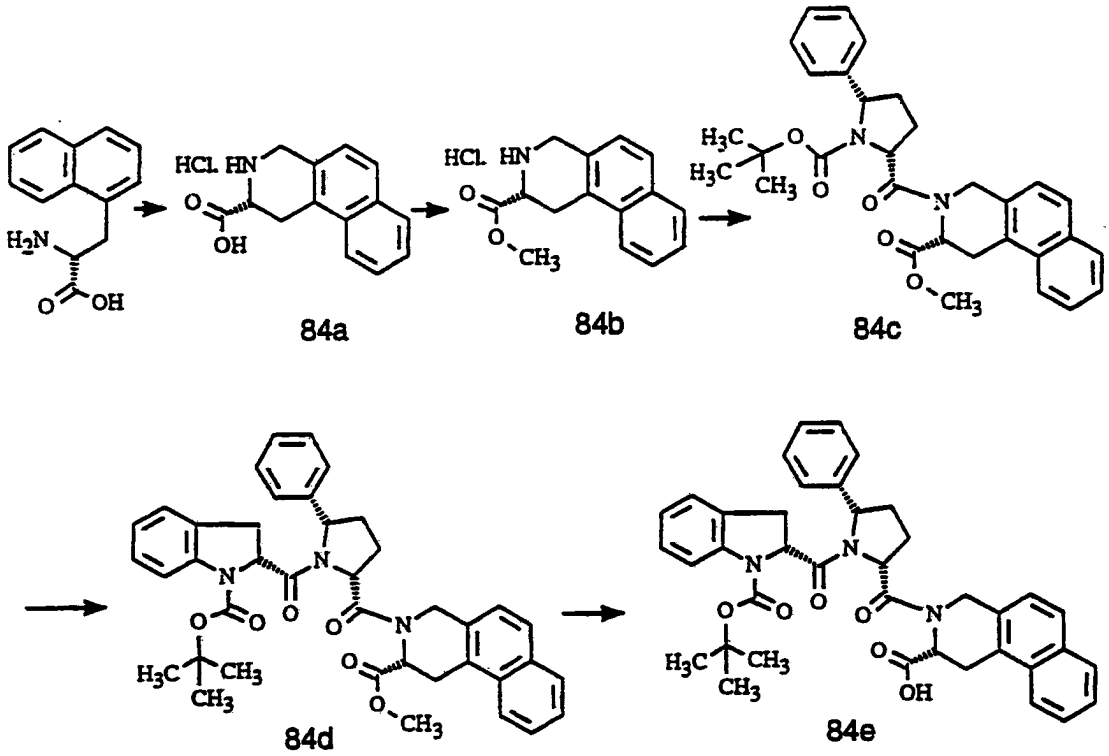
83a Methyl (3R)-2-{(2R,5S)-1-((2R)-1-(2-adamantyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **78b** on a 0.27 mmol scale following the method described for **81a** using 2-adamantanol instead of neopentyl alcohol. The product was isolated in 72% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).

83b (3R)-2-{(2R,5S)-1-((2R)-1-(2-Adamantyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **83a** on a 0.19 mmol scale following the method described for **1f**. The product was isolated in 66% yield (88 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).
HPLC System B t_R=21.4' >99%
Mass spec (FAB) m/e=687 $[M]^+$

EXAMPLE 84



84a (3R)-1,2,3,4-Tetrahydro-benz[*f*]isoquinoline-3-carboxylic acid hydrochloride.

A mixture of D-3-(1-naphthyl)-alanine (5 g, 23.2 mmol), 37% formalin (9 mL) and conc. HCl (40 mL) was heated on a steam bath for 30 min. with occasional swirling. Further formalin (6 mL) and HCl (15 mL) were added and heating was continued for 3 hrs. The mixture was cooled to 4°C and allowed to stand for 2 hrs. The solid product was collected, washed with cold H_2O and acetone, and dried over KOH to give the title compound (3.2 g, 52%).

84b Methyl (3R)-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-carboxylate hydrochloride.

This was prepared from **84a** on a 6.05 mmol scale following the method described for **26a**. The product was isolated in 43% yield after flash chromatography of the free amine on silica gel (eluant EtOAc) and stored as the hydrochloride.

84c Methyl (3R)-2-{(2R,5S)-1-*tert*-butyloxycarbonyl-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-carboxylate.

This was prepared from **67b** and **84b** on a 0.50 mmol scale following the method described for **1d**. The product was isolated in 82% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

84d Methyl (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-carboxylate.

This was prepared from **84c** on a 0.41 mmol scale following the method described for **48b**. The product was isolated in 81% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

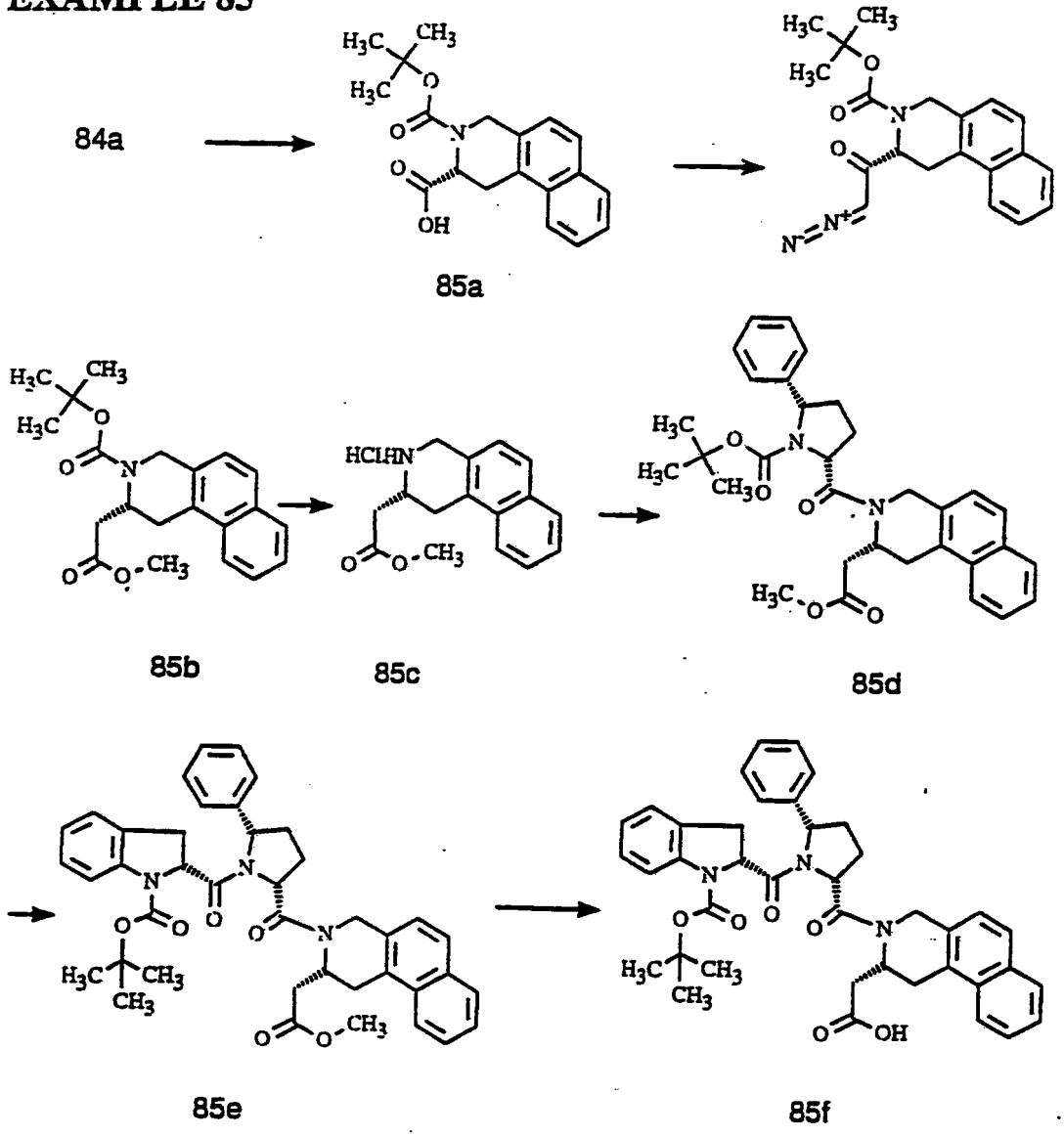
84e (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-carboxylic acid.

This was prepared from **84d** on a 0.33 mmol scale following the method described for **1f**. The product was isolated in 74% yield (157 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 55:45:2 v/v/v).

HPLC System A t_R=23.0' >98%

Mass spec (FAB) m/e=646 $[M+H]^+$

EXAMPLE 85



85a (3R)-2-*tert*-Butyloxycarbonyl-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-carboxylic acid.

This was prepared from 84a on a 6.05 mmol scale following the method described for 1a. The product was isolated in 41% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 35:65:2 v/v/v).

85b Methyl (3R)-2-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-acetate.

This was prepared from **85a** on a 2.5 mmol scale following the method described for **1b**. The intermediate diazoketone was isolated in 80% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v), and the product was isolated in 75% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 18:82 v/v).

85c Methyl (3R)-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-acetate hydrochloride.

This was prepared from **85a** on a 0.49 mmol scale following the method described for **1c**. The product was used without purification assuming a yield of 100%.

85d Methyl (3R)-2-{(2R,5S)-1-*tert*-butyloxycarbonyl-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-acetate.

This was prepared from **67b** and **85c** on a 0.49 mmol scale following the method described for **1d**. The product was isolated in 81% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

85e Methyl (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-acetate.

This was prepared from **85d** on a 0.40 mmol scale following the method described for **48b**. The product was isolated in 87% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

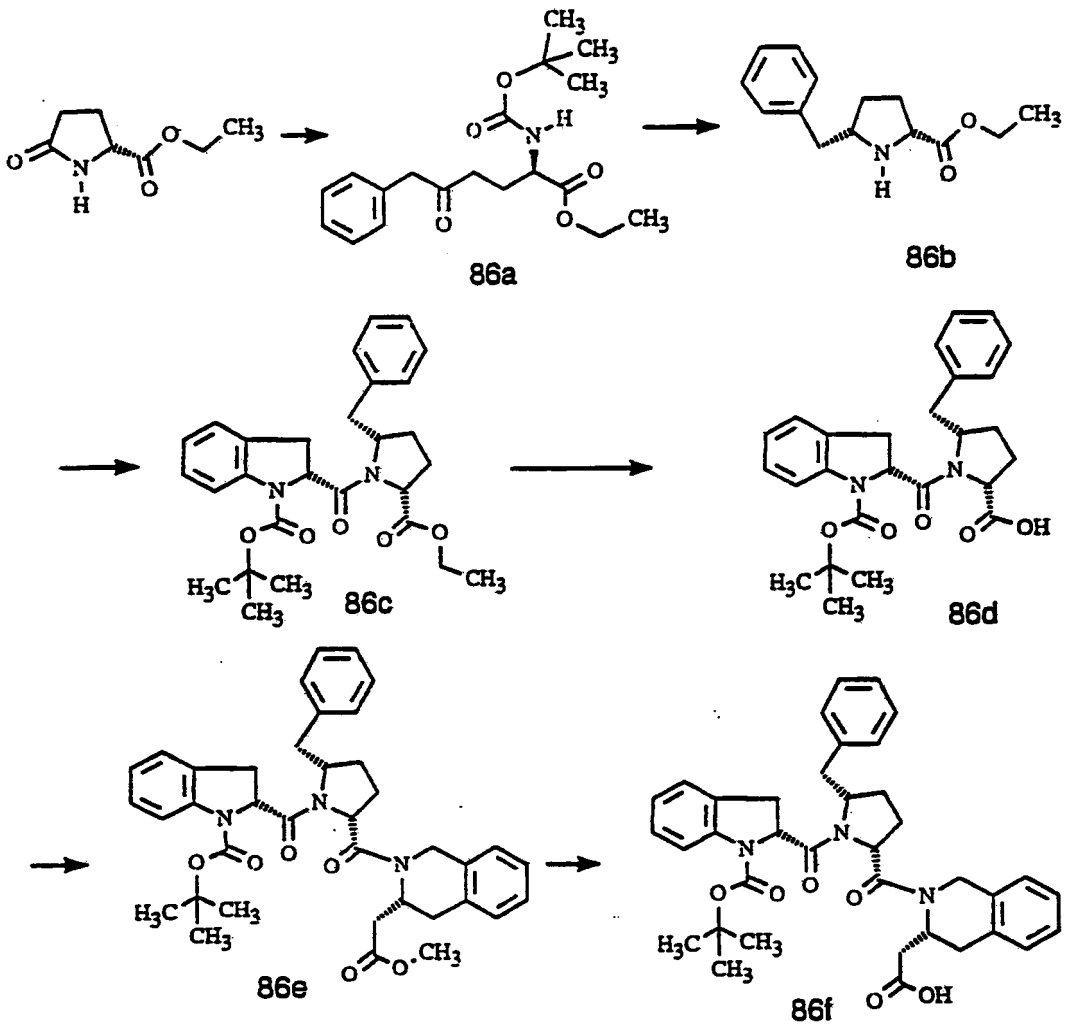
85f (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-acetic acid.

This was prepared from **85e** on a 0.36 mmol scale following the method described for **1f**. The product was isolated in 64% yield (151 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 55:45:2 v/v/v).

HPLC System A t_R=24.1' >99%

Mass spec (FAB) m/e=560 $[M+H\text{-}BOC]^+$

EXAMPLE 86



86a Ethyl (2R)-2-*tert*-butyloxycarbonylamino-5-oxo-6-phenyl-hexanoate.

To a stirred solution of ethyl N-BOC-D-pyroglutamate (2.06 g, 8 mmol) in THF (10 mL), cooled to -78°C under N_2, was added dropwise a solution of benzylmagnesium chloride in THF (5 mL, 2*N*, 10 mmol). The mixture was allowed to warm to room temperature over 1 hr., and was then poured into 5% aq. $KHSO_4$. The mixture was extracted with EtOAc, and the organic phase was washed with satd. $KHCO_3$ and brine, filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v) to give the title compound (1.5 g, 54%).

^{1}H NMR δ 1.28 (3H,t,J=7Hz); 1.47 (9H,s); 3.73 (2H,s); 4.19 (2H,q,J=7Hz)

86b Ethyl (2R,5S)-5-benzyl-pyrrolidine-2-carboxylate.

A solution of **86a** (1.5 g, 4.3 mmol) in CH_2Cl_2 (20 mL) and TFA (20 mL) was stirred at 0°C for 1 hr. then concentrated *in vacuo*, finally with CCl_4 azeotrope. The residue was taken up in EtOH (30 mL). To this solution was added AcOH (3 mL), then diisopropylethylamine (0.87 mL, 5 mmol) and finally $NaBH_3CN$ (0.82 g, 13 mmol) in three portions. The mixture was stirred at room temperature for 3 hr., then the solvent was evaporated *in vacuo*. The residue was partitioned between EtOAc and satd. $KHCO_3$, and the organic phase was washed with brine, filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:pet. ether 60:40 v/v) to give the title compound (410 mg, 41%).
^{1}H NMR δ 1.28 (3H,t,J=7Hz); 2.75 (1H,dd,J=14,7Hz); 2.89 (1H,dd,J=14,7Hz); 4.19 (2H,q,J=7Hz).

86c Ethyl (2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-benzyl-pyrrolidine-2-carboxylate.

This was prepared from **86b** on a 1.76 mmol scale following the method described for **48b**. The product was isolated in 86% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

86d (2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-benzyl-pyrrolidine-2-carboxylic acid.

This was prepared from **86c** on a 1.51 mmol scale following the method described for **1f**. The product was used without purification, assuming a yield of 100%.

86e Methyl (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-benzyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **1c** and **86d** on a 0.50 mmol scale following the method described for **1d**. The product was isolated in 97% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

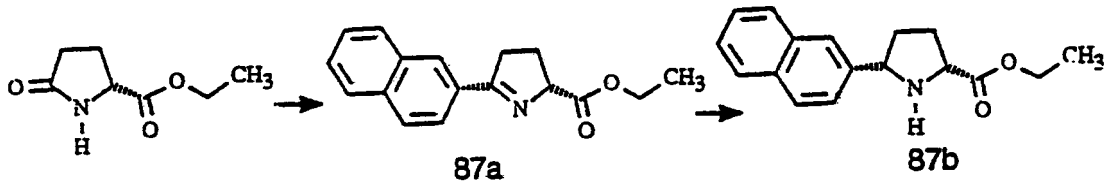
86f (3R)-2-{(2R.5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-5-benzyl-pyrrolidine-2-carbonyl}-1.2.3.4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 86e on a 0.49 mmol scale following the method described for 1f. The product was isolated in 49% yield (150 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:2 v/v/v).

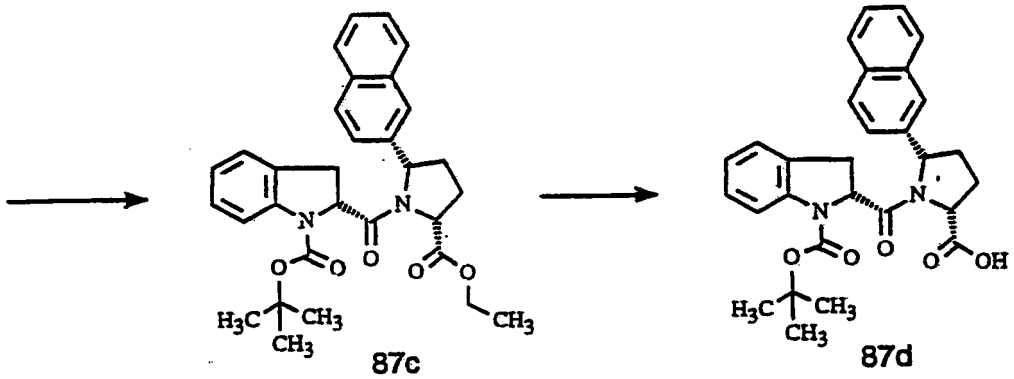
HPLC System A t_R=15.2' >99%

Mass spec (FAB) m/e=624 $[M+H]^+$

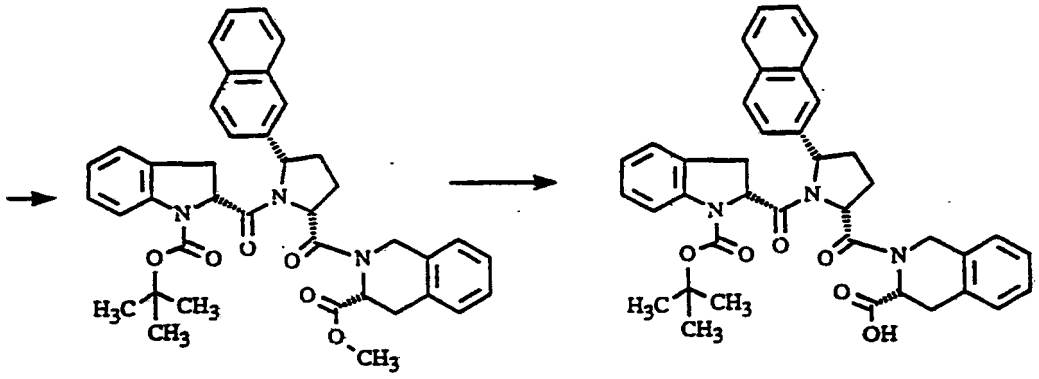
EXAMPLE 87



87a 87b



87c 87d



87e 87f

87a Ethyl (2R)-3,4-dihydro-5-(2-naphthyl)-2H-pyrrole-2-carboxylate.

To a stirred solution of ethyl N-BOC-D-pyroglutamate (2.06 g, 8 mmol) in THF (10 mL), cooled to -78°C under N_2, was added dropwise a solution of 2-naphthylmagnesium chloride in THF (5 mL, 2*N*, 10 mmol). The mixture was allowed to warm to room temperature over 1 hr., and was then poured into 5% aq. $KHSO_4$. The mixture was extracted with EtOAc, and the organic phase was washed with satd. $KHCO_3$ and brine, filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 (20 mL) and TFA (20 mL) and stirred at 0°C for 1 hr. then concentrated *in vacuo*, finally with CCl_4 azeotrope. The residue was taken up in satd. KHCO3 and extracted twice with EtOAc. The combined organic phases were washed with brine, filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 then 40:60 v/v) to give the title compound (605 mg, 28%).
^{1}H NMR δ 1.43 (3H,t,J=7Hz); 4.41 (2H,q,J=7Hz); 5.04 (1H,m)

87b Ethyl (2R,5S)-5-(2-naphthyl)-pyrrolidine-2-carboxylate.

This was prepared from **87a** on a 2.27 mmol scale following the method described for **30a**. The product was isolated in 56% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).
^{1}H NMR δ 1.43 (3H,t,J=7Hz); 4.08 (1H,m); 4.35 (2H,q,J=7Hz); 4.48 (1H,m)

87c Ethyl (2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(2-naphthyl)-pyrrolidine-2-carboxylate.

This was prepared from **87b** on a 1.26 mmol scale following the method described for **48b**. The product was isolated in 99% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

87d (2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(2-naphthyl)-pyrrolidine-2-carboxylic acid.

This was prepared from **87c** on a 1.25 mmol scale following the method described for **1f**. The product was used without purification, assuming a yield of 100%.

87e Methyl (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(2-naphthyl)-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **26a** and **86d** on a 0.31 mmol scale following the method described for **1d**. The product was isolated in 95% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

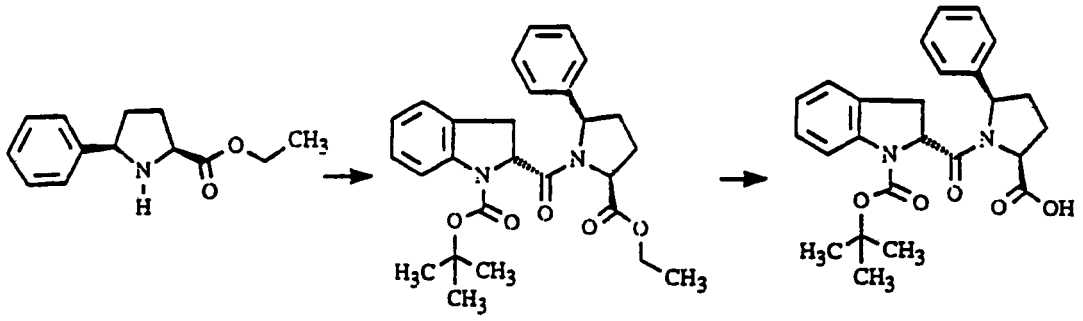
87f (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(2-naphthyl)-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **87e** on a 0.30 mmol scale following the method described for **1f**. The product was isolated in 48% yield (93 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:2 v/v/v).

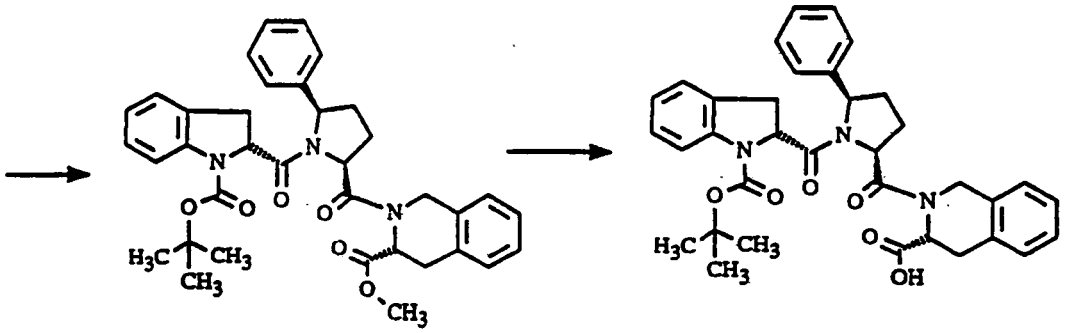
HPLC System A t_R=16.5' >98%

Mass spec (FAB) m/e=646 $[M+H]^+$

EXAMPLE 88



88a 88b



88c 88d

88a Ethyl (2S,5R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carboxylate.

This was prepared from ethyl (2S,5R)-5-phenyl-pyrrolidine-2-carboxylate (the enantiomer of **30a**) following the method described for **48b**. The product was isolated in 97% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).
R_f (EtOAc:hexane 40:60 v/v) 0.27

88b (2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carboxylic acid.

This was prepared from **88a** following the method described for **1f**. The product was isolated in 69% yield and was used without further purification.
R_f (EtOAc:hexane:AcOH 80:20:2 v/v/v) 0.38

88c Methyl (3R)-2-{(2S,5R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **26a** and **88b** on a 0.20 mmol scale following the method described for **1d**. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 50:50 v/v).

R_f (EtOAc:hexane 50:50v/v) 0.24

88d (3R)-2-{(2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

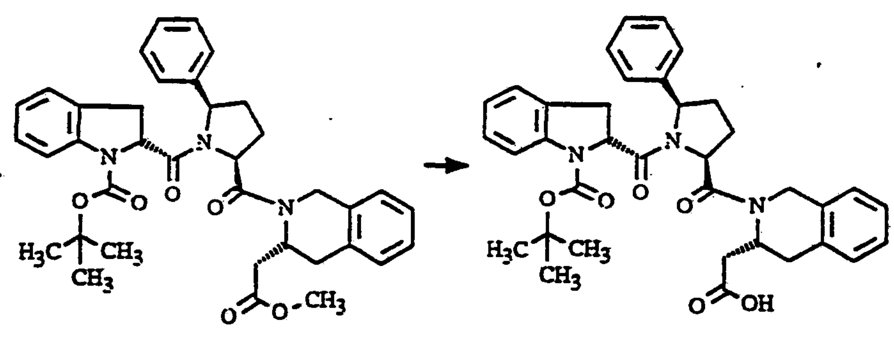
This was prepared from **88c** on a 0.20 mmol scale following the method described for **1f**. The product was isolated in 55% yield (66 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 55:45:2 v/v/v).

HPLC System A t_R=19.8' >98%

Mass spec (FAB) m/e=595 $[M]^+$

EXAMPLE 89

88b →



89a 89b

89a Methyl (3R)-2-{(2S,5R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **1c** and **88b** on a 0.20 mmol scale following the method described for **1d**. The product was isolated in 87% yield after flash chromatography on silica gel (eluant EtOAc:hexane 50:50 v/v).

R_f (EtOAc:hexane 50:50v/v) 0.26

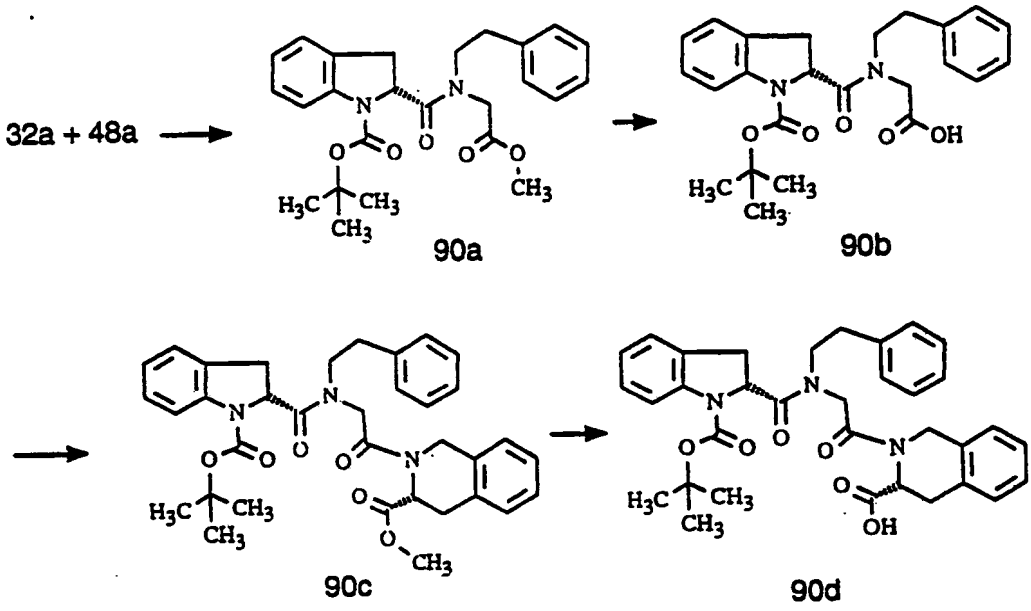
89b (3R)-2-{(2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **89a** on a 0.17 mmol scale following the method described for **1f**. The product was isolated in 53% yield (55 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 55:45:2 v/v/v).

HPLC System A t_R=20.3' >95%

Mass spec (FAB) m/e=610 $[M+H]^+$

EXAMPLE 90



90a Methyl N-phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.

This was prepared from **32a** and **48a** on a 0.70 mmol scale following the method described for **1d**. The product was isolated in 88% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

90b N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from **90a** on a 0.50 mmol scale following the method described for **1f**. The product was used without purification, assuming a yield of 100%.

90c Methyl (3R)-2-{N-phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **90b** and **26a** on a 0.50 mmol scale following the method described for **1d**. The product was isolated in 54% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 35:65:2 v/v/v).

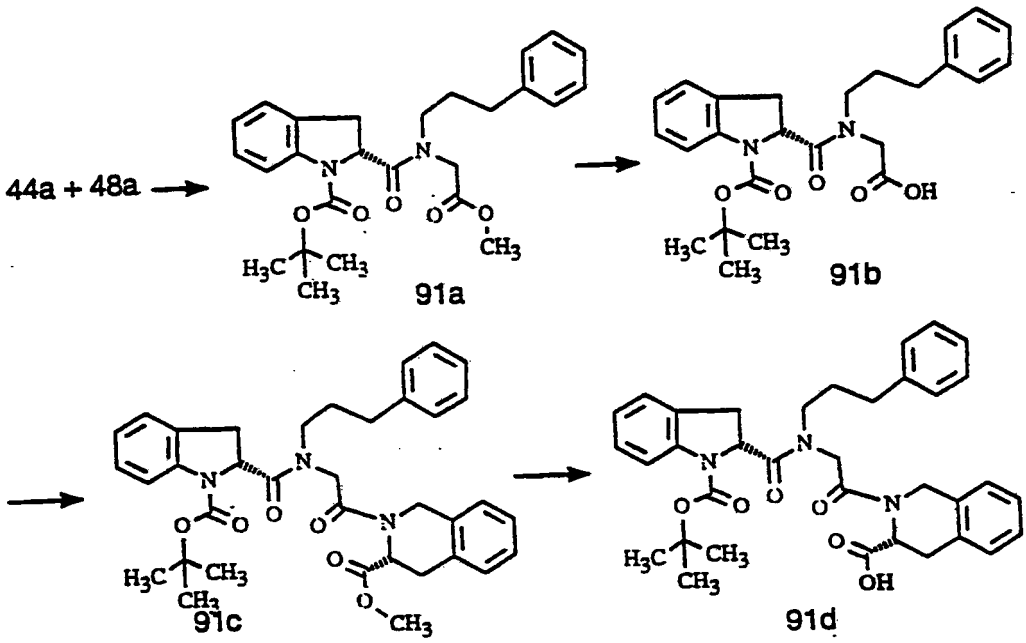
90d (3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **90c** on a 0.27 mmol scale following the method described for **1f**. The product was isolated in 72% yield (114 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 55:45:2 v/v/v).

HPLC System A t_R=19.9' >99%

Mass spec (FAB) m/e=584 $[M+H]^+$

EXAMPLE 91



91a Methyl N-3-phenylpropyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.

This was prepared from **44a** and **48a** on a 3.52 mmol scale following the method described for **1d**. The product was isolated in 55% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R_f (EtOAc:hexane 40:60 v/v) 0.31

91b N-3-Phenylpropyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from **91a** on a 0.98 mmol scale following the method described for **1f**. The product was used without purification, assuming a yield of 100%.

91c Methyl (3R)-2-{N-3-phenylpropyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **26a** and **91b** on a 0.98 mmol scale following the method described for **1d**. The product was isolated in 25% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R_f (EtOAc:hexane 40:60 v/v) 0.17

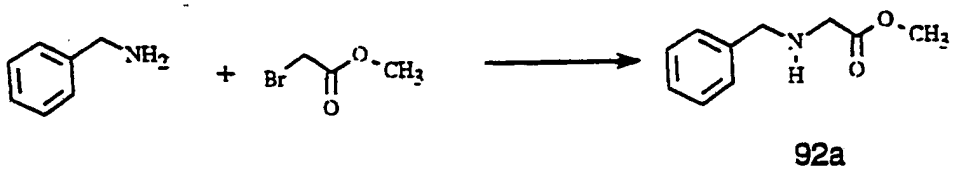
91d (3R)-2-{N-3-Phenylpropyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **91c** on a 0.25 mmol scale following the method described for **1f**. The product was isolated in 43% yield (65 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 70:30:1 v/v/v).

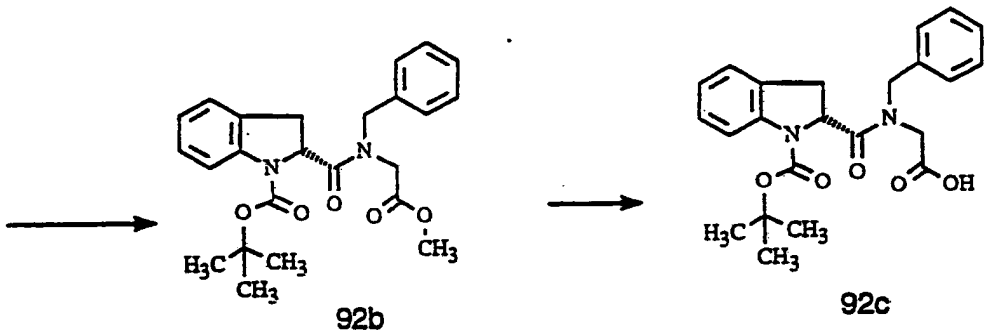
HPLC System A t_R=20.1' >98%

Mass spec (FAB) m/e=598 $[M+H]^+$

EXAMPLE 92

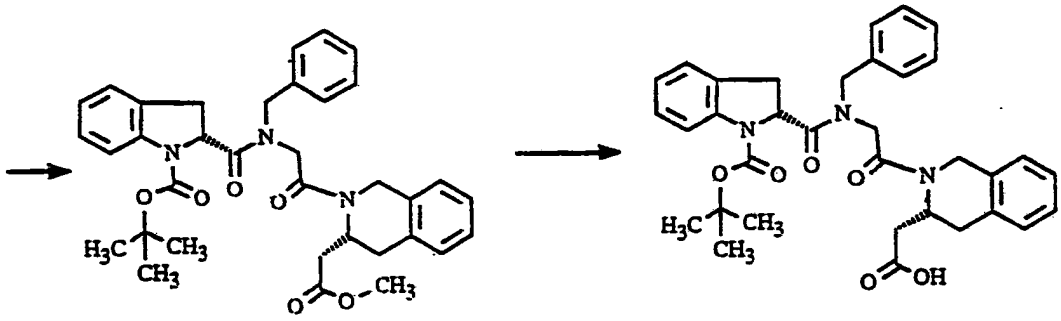


92a



92b

92c



92d

92e

92a Methyl N-benzyl-glycinate.

This was prepared from benzylamine on a 4.58 mmol scale following the method described for **32a**. The product was isolated in 95% yield and used without further purification.

92b Methyl N-benzyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.

This was prepared from **92a** and **48a** on a 4.37 mmol scale following the method described for **1d**. The product was isolated in 65% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R_f (EtOAc:hexane 40:60 v/v) 0.38

92c N-Benzyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from **92b** on a 1.43 mmol scale following the method described for **1f**. The product was used without purification, assuming a yield of 100%.

92d Methyl (3R)-2-{N-benzyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **1c** and **92c** on a 1.43 mmol scale following the method described for **1d**. The product was isolated in 75% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R_f (EtOAc:hexane 40:60 v/v) 0.18

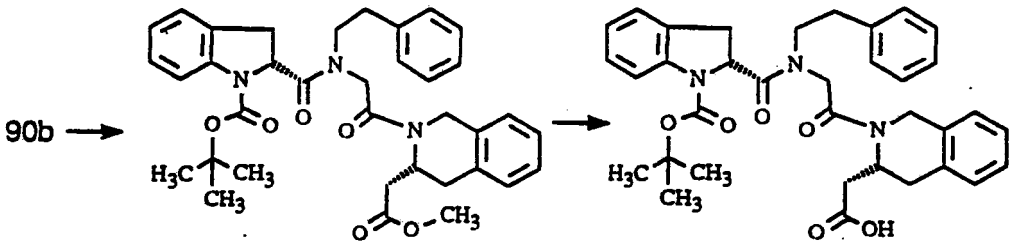
92e (3R)-2-{N-Benzyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **92d** on a 1.07 mmol scale following the method described for **1f**. The product was isolated in 59% yield (374 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 65:35:1 v/v/v).

HPLC System A t_R=19.4' >95%

Mass spec (FAB) m/e=584 $[M+H]^+$

EXAMPLE 93



93a Methyl (3R)-2-{N-phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **1c** and **90b** on a 0.41 mmol scale following the method described for **1d**. The product was isolated in 83% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

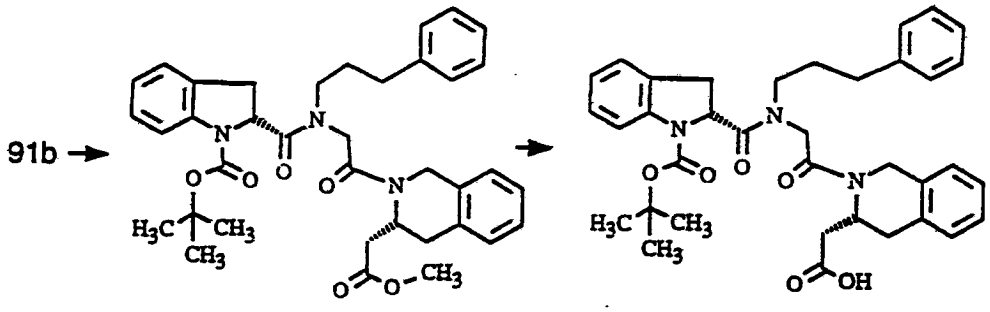
93b (3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **93a** on a 0.34 mmol scale following the method described for **1f**. The product was isolated in 54% yield (110 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 40:60:2 v/v/v).

HPLC System B t_R=15.0' >95%

Mass spec (FAB) m/e=598 $[M+H]^+$

EXAMPLE 94



94a Methyl (3R)-2-{N-3-Phenylpropyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **1c** and **91b** on a 0.98 mmol scale following the method described for **1d**. The product was isolated in 68% yield after flash chromatography on silica gel (eluant EtOAc:hexane 45:55 v/v).

R_f (EtOAc:hexane 45:55 v/v) 0.15

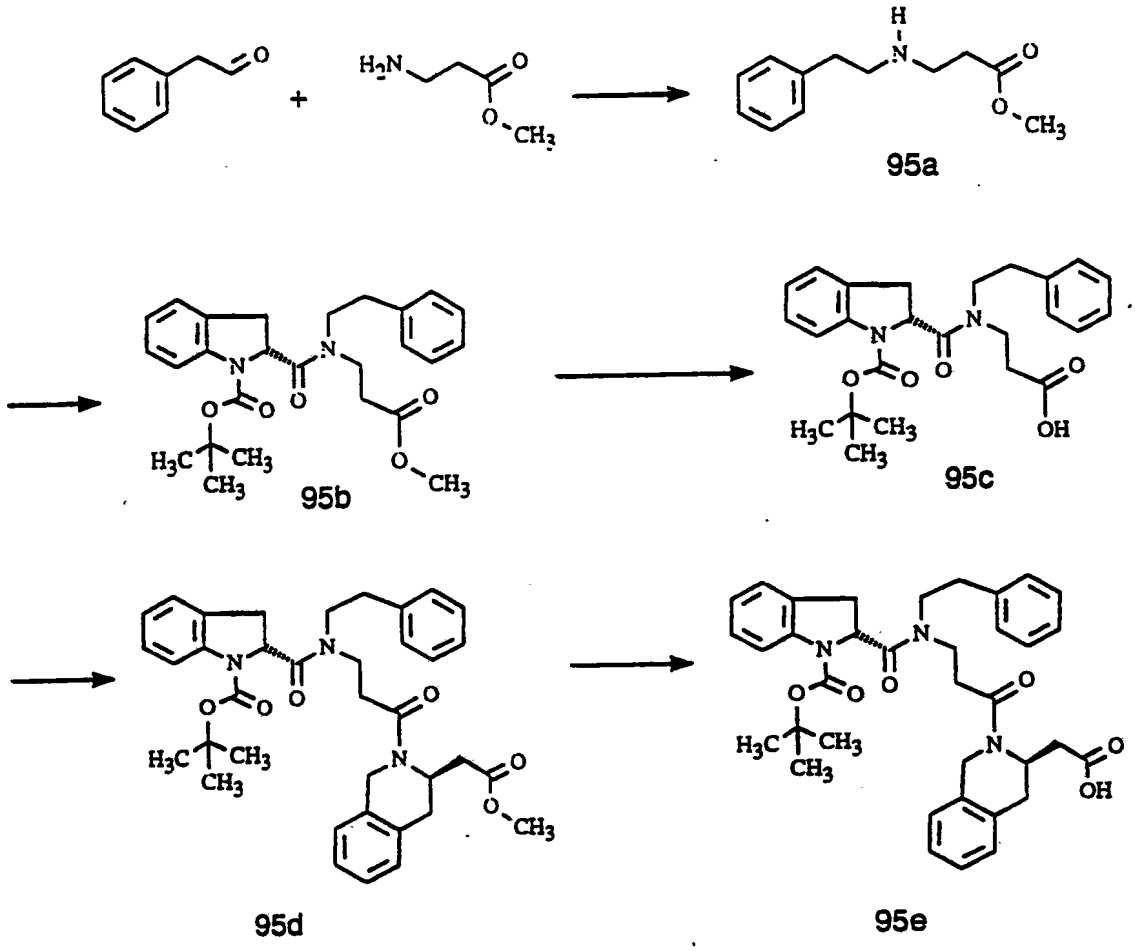
94b (3R)-2-{N-3-Phenylpropyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **94a** on a 0.67 mmol scale following the method described for **1f**. The product was isolated in 55% yield (228 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 60:40:1 v/v/v).

HPLC System A t_R=21.0' >98%

Mass spec (FAB) m/e=611 $[M]^+$

EXAMPLE 95



95a Methyl 3-phenethylamino-propanoate.

This was prepared from phenylacetaldehyde and β-alanineOMe on a 2.25 mmol scale following the method described for **42a**. The product was isolated in 40% yield after flash chromatography on silica gel (eluant $CHCl_3$:MeOH:AcOH 35:2:1 v/v/v).

95b Methyl 3-{N-phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-amino}-propanoate.

This was prepared from **40a** and **95a** on a 0.92 mmol scale following the method described for **1d**. The product was isolated in 63% yield after flash chromatography on silica gel (eluant EtOAc:hexane 25:75 v/v).

95c 3-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-amino}-propanoic acid.

This was prepared from **95b** on a 0.59 mmol scale following the method described for **1f**. The product was isolated in 54% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 50:50:1 v/v/v).

HPLC System A t_R=15.9' >98%

Mass spec (FAB) m/e=439 $[M+H]^+$

95d Methyl (3R)-2-{3-{N-phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-amino}-propanoyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **26a** and **95c** on a 0.15 mmol scale following the method described for **1d**. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 60:40 v/v).

R_f (EtOAc:hexane 70:30 v/v) 0.38

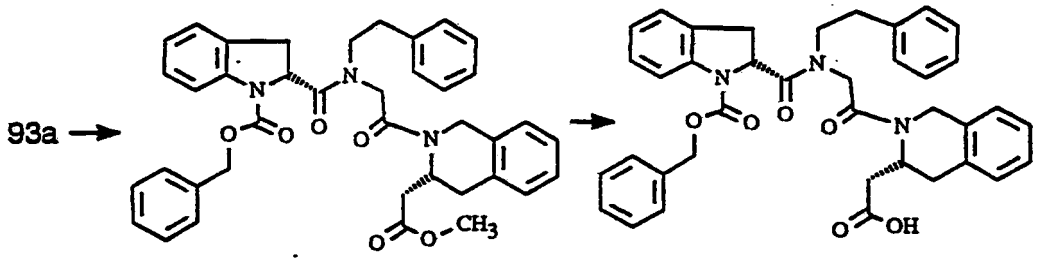
95e (3R)-2-{3-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-amino}-propanoyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **95d** on a 0.15 mmol scale following the method described for **1f**. The product was isolated in 56% yield (50 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System A t_R=19.3' >95%

Mass spec (FAB) m/e=598 $[M+H]^+$

EXAMPLE 96



96a Methyl(3R)-2-{N-phenethyl-N-((2R)-1-benzyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 93a and benzyl chloroformate on a 0.46 mmol scale following the method described for 81a. The product was isolated in 100% yield and used without further purification.

R_f (EtOAc:pet. ether 40:60 v/v) 0.17

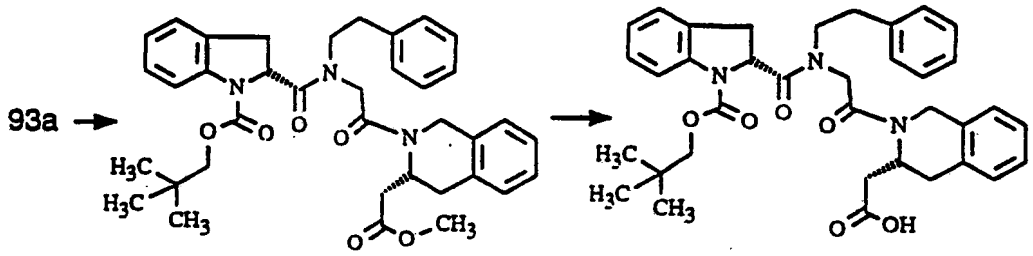
96b (3R)-2-{N-Phenethyl-N-((2R)-1-benzyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 96a on a 0.46 mmol scale following the method described for 1f. The product was isolated in 67% yield (194 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 55:45:1 v/v/v).

HPLC System B t_R=14.8' >98%

Mass spec (FAB) m/e=441 $[M+H-Cmt]^+$

EXAMPLE 97



97a Methyl (3R)-2-{N-phenethyl-N-((2R)-1-neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 93a on a 0.46 mmol scale following the method described for 81a. The product was isolated in 100% yield and used without further purification.

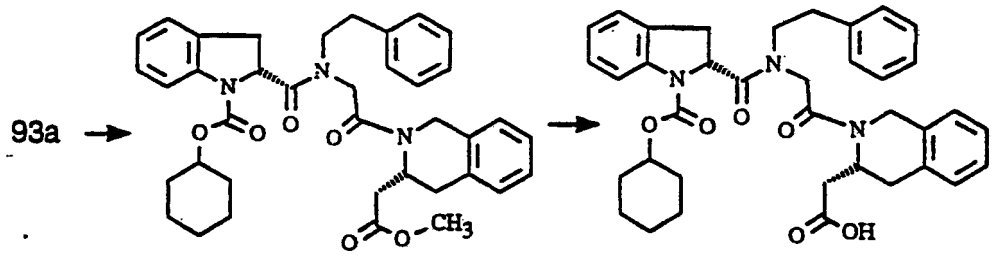
R_f (EtOAc:pet. ether 40:60 v/v) 0.21

97b (3R)-2-{N-Phenethyl-N-((2R)-1-neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 97a on a 0.46 mmol scale following the method described for 1f. The product was isolated in 35% yield (101 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:1 v/v/v).

HPLC System B t_R=16.2' >90%
Mass spec (FAB) m/e=612 $[M+H]^+$

EXAMPLE 98



98a 98b

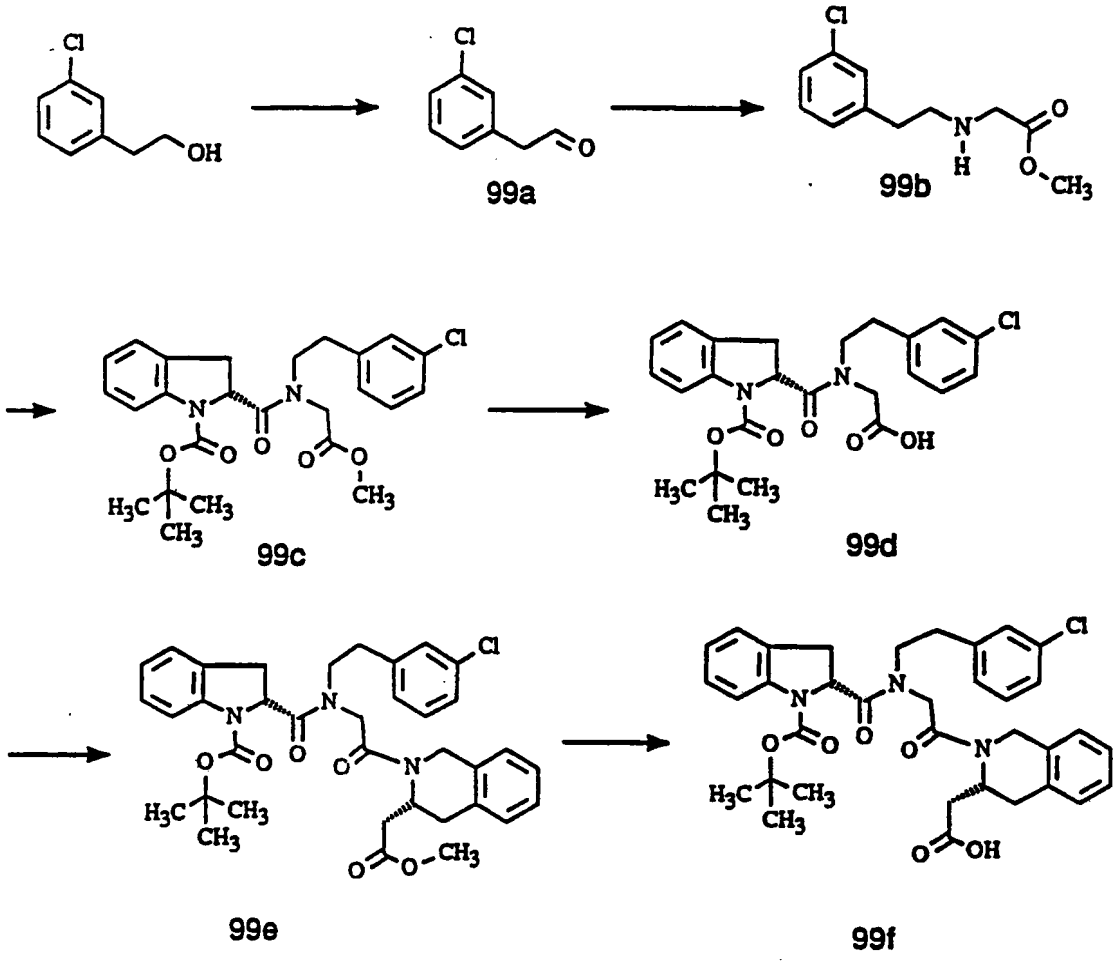
98a Methyl (3R)-2-{N-phenethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **93a** on a 0.46 mmol scale following the method described for **82a**. The product was isolated in 100% yield and used without further purification.

98b (3R)-2-{N-Phenethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **98a** on a 0.46 mmol scale following the method described for **1f**. The product was isolated in 25% yield (74 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:1 v/v/v).
HPLC System B t_R=17.6' >90%
Mass spec (FAB) m/e=624 $[M+H]^+$

EXAMPLE 99



99a 3-Chlorophenylacetaldehyde.

This was prepared from 3-chlorophenethyl alcohol on a 9.58 mmol scale using the standard Swern oxidation conditions (A.J. Mancuso *et al*, *J.Org.Chem.*, **43**, 2480, 1978). The product was used without purification assuming a yield of 100%.

99b Methyl N-3-chlorophenethyl-glycinate.

This was prepared from **99a** on a 9.58 mmol scale following the method described for **42a**. The product was isolated in 5.5% yield after flash chromatography on silica gel (eluant EtOAc:hexane 80:20 v/v).

99c Methyl N-3-chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.

This was prepared from **99b** and **48a** on a 0.50 mmol scale following the method described for **1d**. The product was isolated in 47% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

R_f (EtOAc:hexane 40:60 v/v) 0.29

99d N-3-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from **99c** on a 0.24 mmol scale following the method described for **1f**. The product was used without purification, assuming a yield of 100%.

99e Methyl (3R)-2-{N-3-chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **1c** and **99d** on a 0.12 mmol scale following the method described for **1d**. The product was isolated in 23% yield after flash chromatography on silica gel (eluant EtOAc:hexane 45:55 v/v).

R_f (EtOAc:hexane 50:50 v/v) 0.25

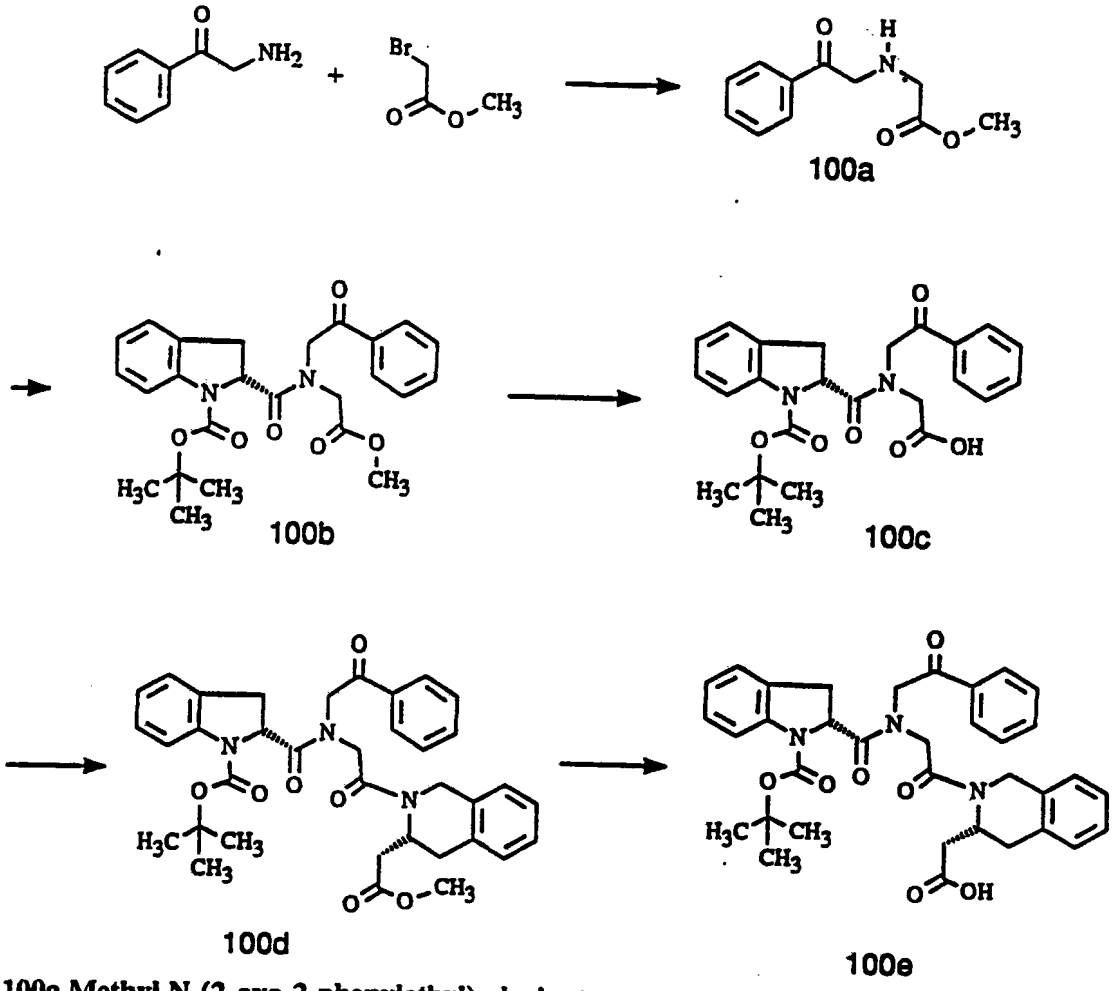
99f (3R)-2-{N-3-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **99e** on a 0.028 mmol scale following the method described for **1f**. The product was isolated in 71% yield (12 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 65:35:2 v/v/v).

HPLC System A t_R=22.0' >80%

Mass spec (FAB) m/e=632 $[M+H]^+$

EXAMPLE 100



100a Methyl N-(2-oxo-2-phenylethyl)-glycinate.

This was prepared from 2'-aminoacetophenone hydrochloride on a 11.6 mmol scale following the method described for **32a**. The product was isolated in 83% yield after flash chromatography on silica gel (eluant EtOAc:pet.ether 90:10).

^{1}H NMR δ 3.56 (2H,s); 3.70 (3H,s); 4.20 (2H,s); 7.4-7.6 (3H,m); 7.9-8.0 (2H,m)

100b Methyl N-(2-oxo-2-phenylethyl)-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.

This was prepared from **100a** and **48a** on a 0.97 mmol scale following the method described for **1d**. The product was isolated in 62% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

R_f (EtOAc:pet. ether 35:65 v/v) 0.31

^{1}H NMR δ 1.56 (9H,2s); 3.74 (3H,2s)

100c N-(2-Oxo-2-phenylethyl)-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from **100b** on a 0.61 mmol scale following the method described for **1f**. The product was isolated in 84% yield and used without further purification.

100d Methyl (3R)-2-{N-(2-oxo-2-phenylethyl)-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **1c** and **100c** on a 0.52 mmol scale following the method described for **1d**. The product was isolated in 49% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:1 v/v/v).

^{1}H NMR δ 1.56 (9H,3s); 3.55 (3H,2s)

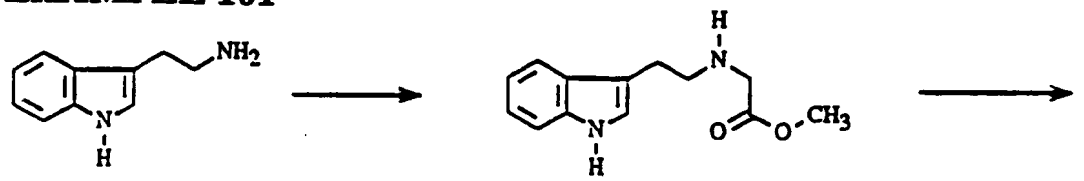
100e (3R)-2-{N-(2-Oxo-2-phenylethyl)-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **100d** on a 0.26 mmol scale following the method described for **1f**. The product was isolated in 71% yield (113 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 70:30:1 v/v/v).

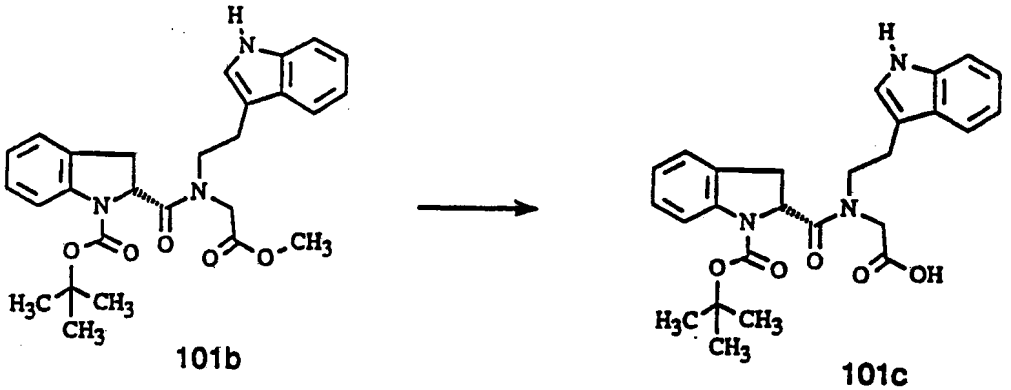
HPLC System B t_R=13.4' >98%

Mass spec (FAB) m/e=612 $[M+H]^+$

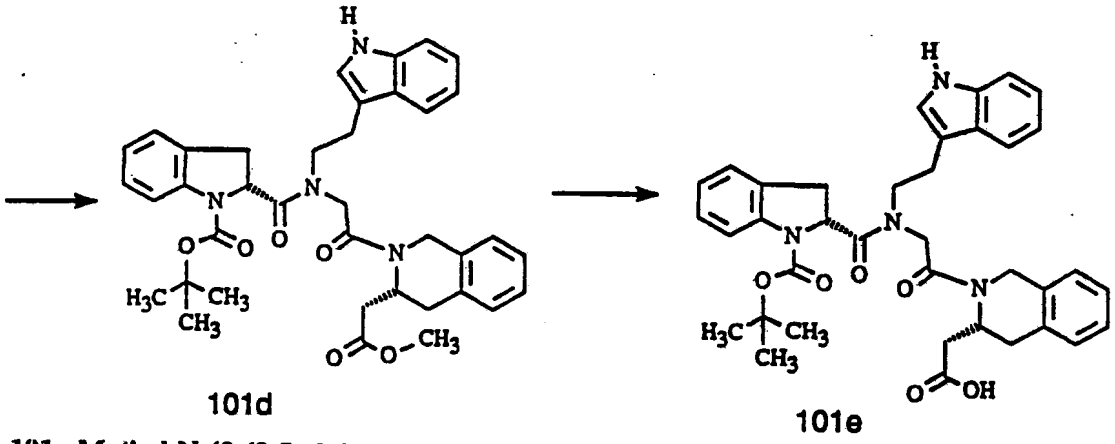
EXAMPLE 101



101a



101b 101c



101d 101e

101a Methyl N-(2-(3-Indolyl)ethyl)-glycinate.

This was prepared from tryptamine hydrochloride on a 5.0 mmol scale following the method described for **32a**. The product was used without purification, assuming a yield of 100%.

101b Methyl N-(2-(3-Indolyl)ethyl)-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.

This was prepared from **101a** and **48a** on a 1.0 mmol scale following the method described for **1d**. The product was isolated in 44% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).

101c N-(2-(3-Indolyl)ethyl)-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from **101b** on a 0.44 mmol scale following the method described for **1f**. The product was isolated in 40% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).
HPLC System A t_R=10.5' >99%
Mass spec (FAB) m/e=464 $[M+H]^+$

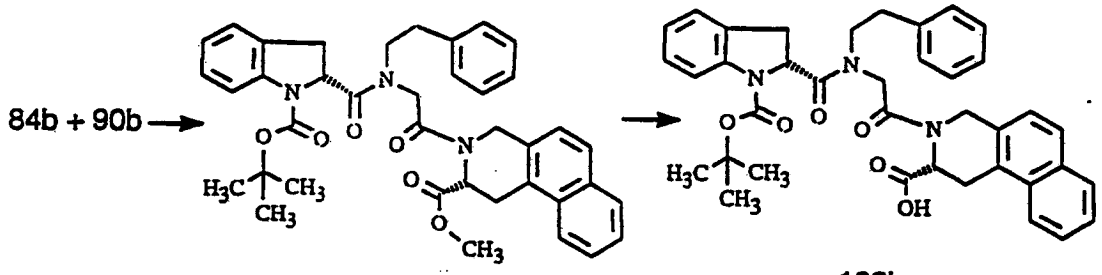
101d Methyl (3R)-2-{N-(2-(3-indolyl)ethyl)-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **1c** and **101d** on a 0.08 mmol scale following the method described for **1d**. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 55:45 v/v).
R_f (EtOAc:hexane 55:45 v/v) 0.30

101e (3R)-2-{N-(2-(3-Indolyl)ethyl)-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **101d** on a 0.08 mmol scale following the method described for **1f**. The product was isolated in 56% yield (28 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 70:30:2 v/v/v).
HPLC System A t_R=18.2' >95%
Mass spec (FAB) m/e=659 $[M+Na]^+$

EXAMPLE 102



102a Methyl (3R)-2-{N-phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-carboxylate.

This was prepared from **90b** and **84b** on a 0.46 mmol scale following the method described for **1d**. The product was isolated in 69% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

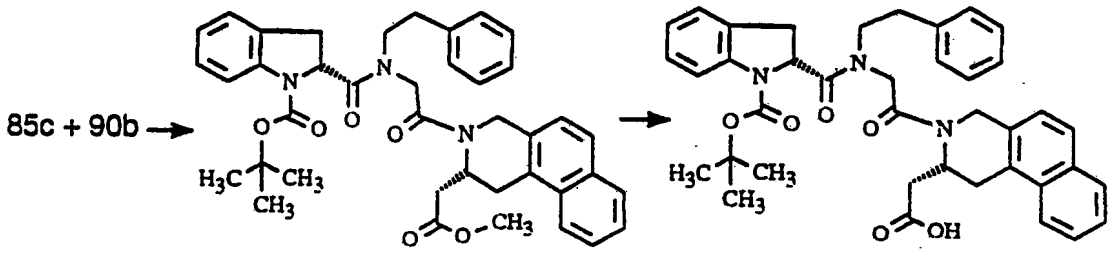
102b (3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-carboxylic acid.

This was prepared from **102a** on a 0.32 mmol scale following the method described for **1f**. The product was isolated in 68% yield (138 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:2 v/v/v).

HPLC System A t_R=22.1' >98%

Mass spec (FAB) m/e=634 $[M+H]^+$

EXAMPLE 103



103a 103b

103a Methyl (3R)-2-{N-phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-acetate.

This was prepared from **90b** and **85c** on a 0.48 mmol scale following the method described for **1d**. The product was isolated in 85% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

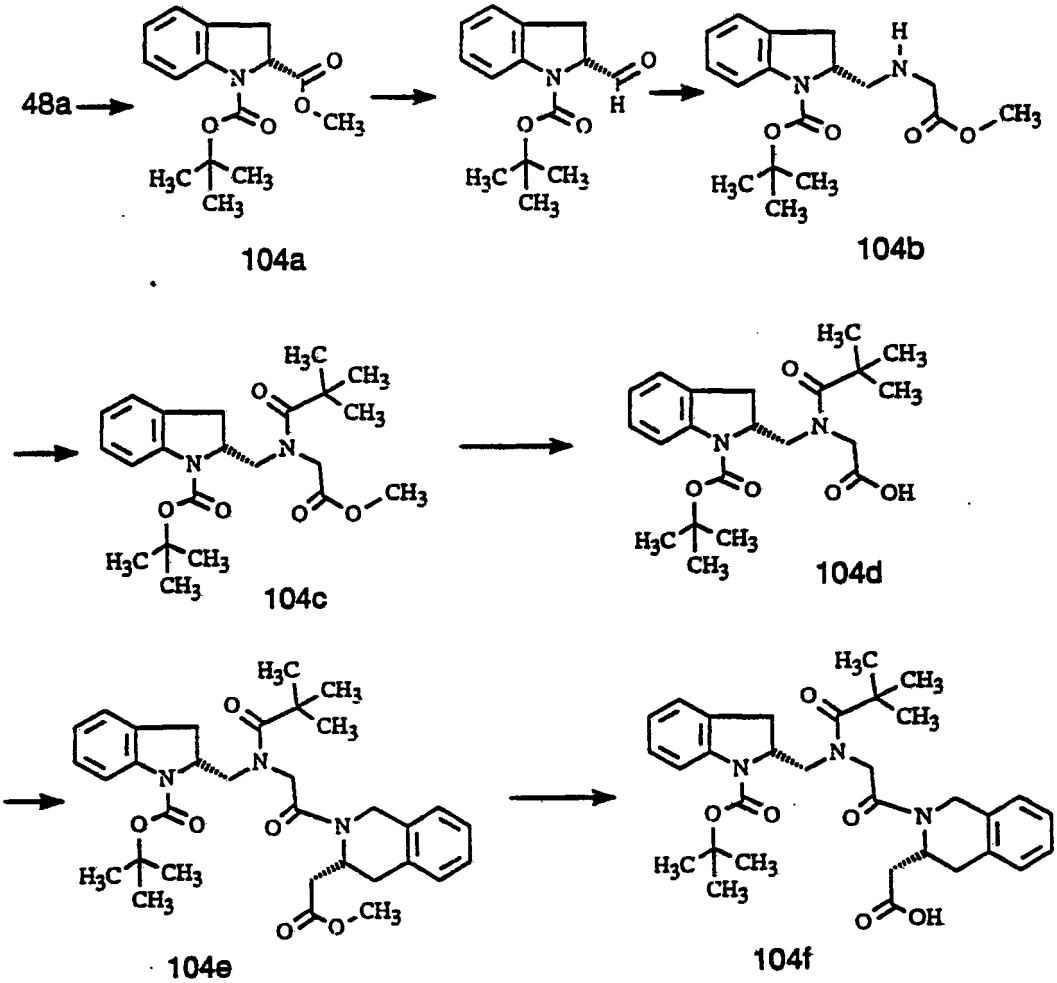
103b (3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-acetic acid.

This was prepared from **103a** on a 0.41 mmol scale following the method described for **1f**. The product was isolated in 74% yield (196 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 55:45:2 v/v/v).

HPLC System A t_R=22.4' >98%

Mass spec (FAB) m/e=648 $[M+H]^+$

EXAMPLE 104



104a Methyl (2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carboxylate.

To a stirred solution of 48a (1.05 g, 4 mmol) and 4-dimethylaminopyridine (50 mg, 0.4 mmol) in CH_2Cl_2 (20 mL) and MeOH (10 mL) was added WSCD.HCl (1.54 g, 8 mmol). The mixture was stirred at room temperature for 3 hrs. and then concentrated *in vacuo*. The residue was partitioned between EtOAc and H_2O, and the organic phase was washed with 10% $KHSO_4$, satd. $KHCO_3$ and brine. filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo* to give the title compound (0.89 g, 80%) as an oil which was used without further purification.

104b Methyl N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-methyl)-glycinate.

This was prepared from **104a** and GlyOMe on a 3.2 mmol scale following the method described for **31a**. The product was isolated in 33% yield after flash chromatography on silica gel (eluant EtOAc:hexane 20:80 then 40:60 v/v).

R_f (EtOAc:hexane 25:75 v/v) 0.08

104c Methyl N-pivaloyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-methyl)-glycinate.

To an ice-cold stirred solution of **104b** (70 mg, 0.22 mmol) and diisopropylethylamine (0.15 mL, 0.9 mmol) in CH_2Cl_2 (10 mL) was added pivaloyl chloride (80 mL, 0.66 mmol). The mixture was stirred at 0°C for 2 hrs. and then concentrated *in vacuo*. The residue was partitioned between EtOAc and H_2O, and the organic phase was washed with 10% $KHSO_4$, satd. $KHCO_3$ and brine, filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v) to give the title compound (67 mg, 75%).

R_f (EtOAc:hexane 50:50 v/v) 0.34

104d N-Pivaloyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-methyl)-glycine.

This was prepared from **104c** on a 0.17 mmol scale following the method described for **1f**. The product was used without purification, assuming a yield of 100%.

104e Methyl (3R)-2-{N-pivaloyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-methyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **104d** and **1c** on a 0.17 mmol scale following the method described for **1d**. The product was isolated in 65% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R_f (EtOAc:hexane 50:50 v/v) 0.25

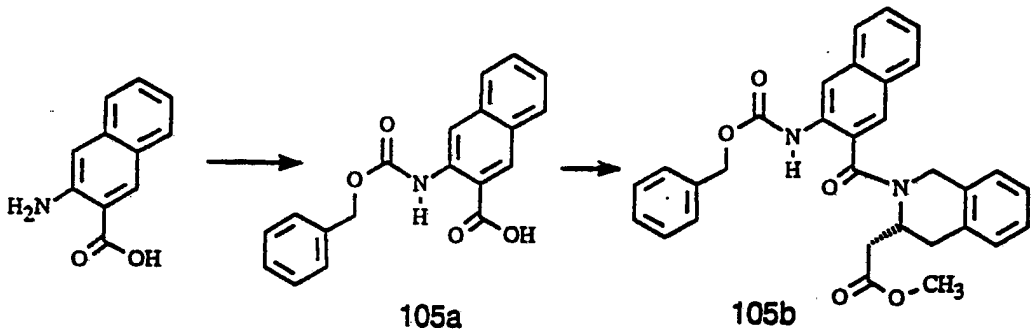
104f (3R)-2-{N-Pivaloyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-methyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **104e** on a 0.11 mmol scale following the method described for **1f**. The product was isolated in 50% yield (31 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 60:40:1 v/v/v).

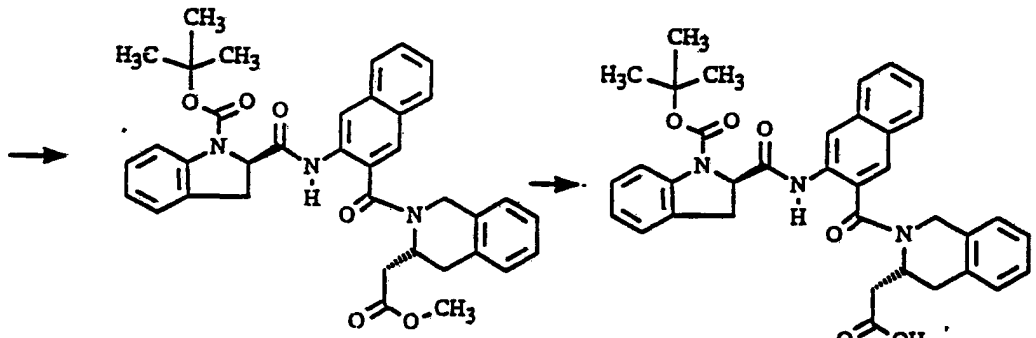
HPLC System A t_R=18.0' >98%

Mass spec (FAB) m/e=564 $[M+H]^+$

EXAMPLE 105



105a 105b



105c 105d

105a 3-(Benzyloxycarbonylamino)-naphthalene-2-carboxylic acid.

To a stirred suspension of 3-aminonaphthalene-2-carboxylic acid (4.22 g, 22.5 mmol) in H_2O (37.5 mL) was added *5N* NaOH (4.95 mL, 24.8 mmol). The resulting solution was cooled in ice then treated alternately with benzyl chloroformate (4 mL, 28.3 mmol) and *2N* NaOH (14 mL, 28 mmol) in five equal portions. Acetonitrile (50 mL) was added and the mixture was stirred at room temperature overnight then concentrated *in vacuo*. The residue was partitioned between EtOAc and 0.3*M* $KHSO_4$, and the organic phase was washed with 0.3*M* $KHSO_4$, H_2O and brine, filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo*. The residue was purified by recrystallisation from acetonitrile to give the title compound (3.09 g, 42%).

105b Methyl (3R)-2-{3-(benzyloxycarbonylamino)-naphthalene-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **105a** and **1c** on a 0.78 mmol scale following the method described for **1d**. The product was isolated in 76% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

105c Methyl (3R)-2-{3-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonylamino)-naphthalene-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **105b** and **1c** on a 0.59 mmol scale following the method described for **1d**. The starting material **105b** was deprotected prior to coupling by catalytic hydrogenolysis over 5% Pd-on-C in 1% v/v AcOH/MeOH as solvent for 90 min. The product was isolated in 66% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

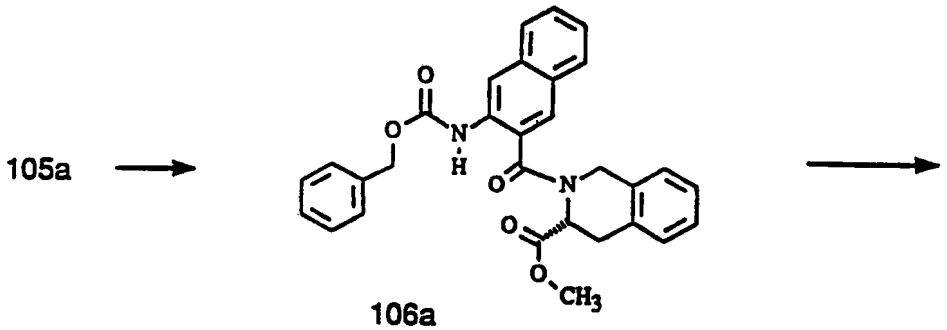
105d (3R)-2-{3-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonylamino)-naphthalene-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

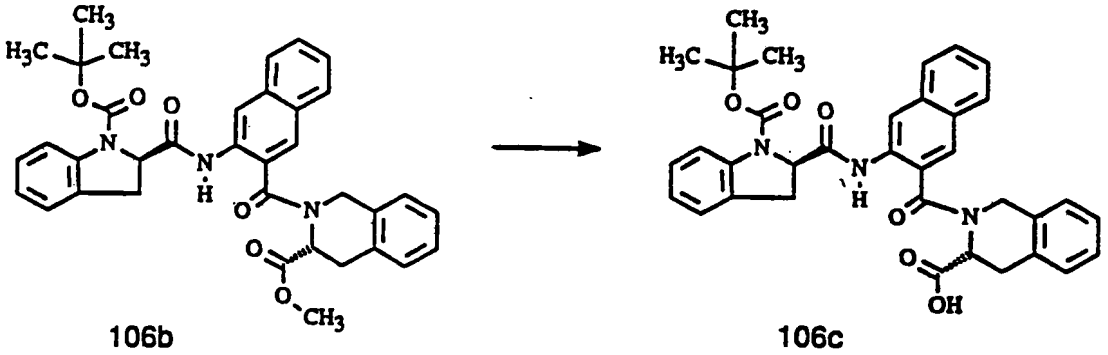
This was prepared from **105c** on a 0.39 mmol scale following the method described for **1f**. The product was isolated in 52% yield (123 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).

HPLC System B t_R=14.2' >95%

Mass spec (FAB) m/e=606 $[M+H]^+$

EXAMPLE 106





106a Methyl (3R)-2-{3-(benzyloxycarbonylamino)-naphthalene-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **105a** and **26a** on a 1.22 mmol scale following the method described for **1d**. The product was isolated in 64% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

106b Methyl (3R)-2-{3-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonylamino)-naphthalene-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **106a** and **48a** on a 0.78 mmol scale following the method described for **105c**. The product was isolated in 47% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

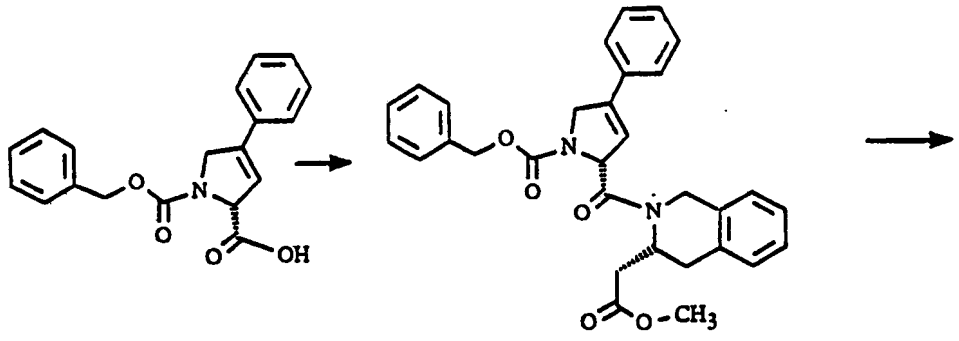
106c (3R)-2-{3-((2R)-1-*tert*-Butyloxycarbonyl-2.3-dihydroindole-2-carbonylamino)-naphthalene-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **106b** on a 0.38 mmol scale following the method described for **1f**. The product was isolated in 70% yield (159 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 70:30:1 v/v/v).

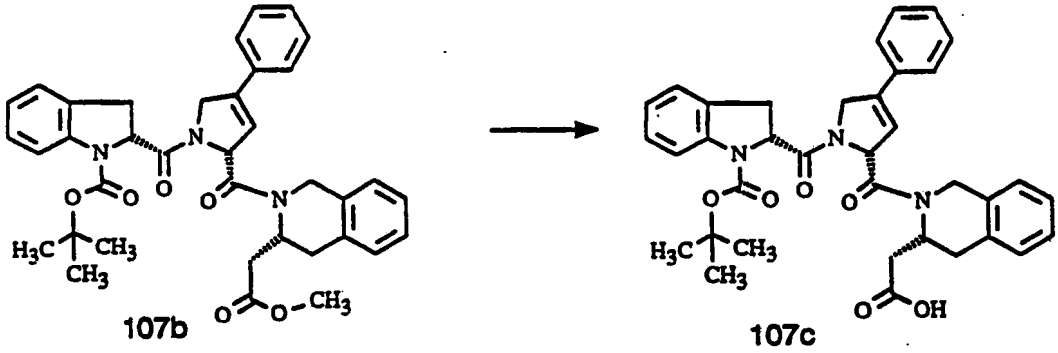
HPLC System B t_R=14.1' >95%

Mass spec (FAB) m/e=592 $[M+H]^+$

EXAMPLE 107



107a



107b 107c

107a Methyl (3R)-2-{(2R)-1-benzyloxycarbonyl-4-phenyl-2,5-dihydropyrrole-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **1c** on a 1.3 mmol scale following the method described for **1d** using (2R)-1-benzyloxycarbonyl-4-phenyl-2,5-dihydropyrrole-2-carboxylic acid (J. Krapcho *et al*, *J.Med.Chem.*, **31**, 1148, 1988) instead of N-BOC-O-benzyl-threonine. The product was isolated in 48% yield after flash chromatography on silica gel (eluant EtOAc:hexane 55:45 v/v)

107b Methyl (3R)-2-{(2R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenyl-2,5-dihydropyrrole-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **107a** and **48a** on a 0.63 mmol scale following the method described for **1d**. The starting material **107a** was deprotected prior to coupling by treatment with 45% HBr in AcOH for 90 min. The product was isolated in 27% yield after flash chromatography on silica gel (eluant EtOAc:hexane 30:70 v/v).

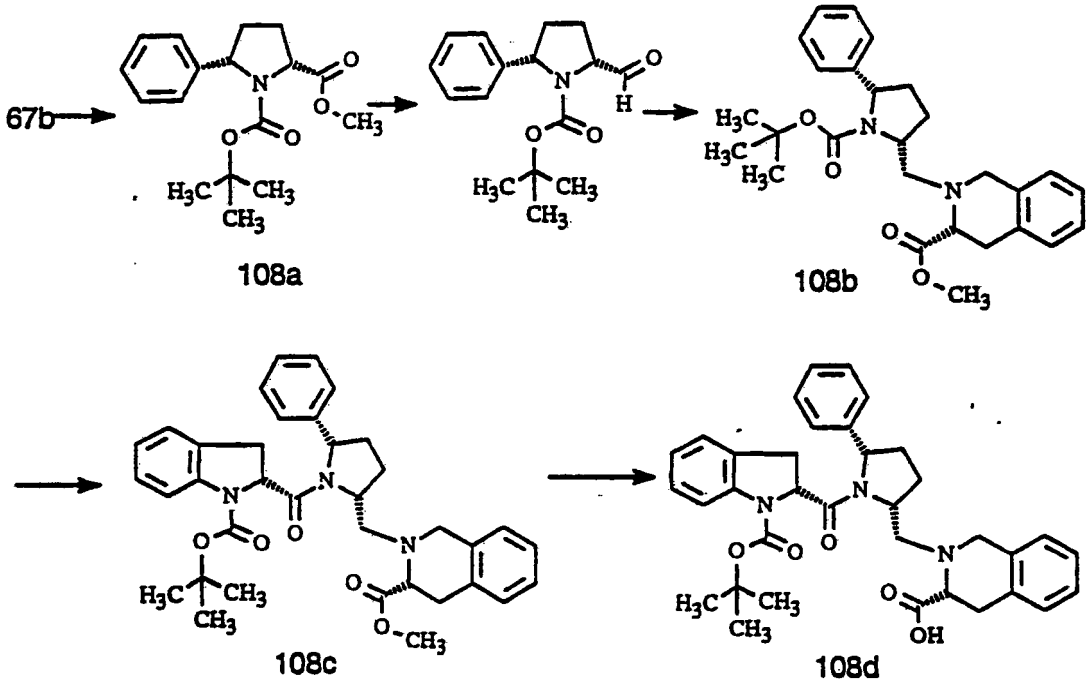
107c (3R)-2-{(2R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenyl-2,5-dihydropyrrole-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **107b** on a 0.17 mmol scale following the method described for **1f**. The product was isolated in 40% yield (41 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 40:60:2 v/v/v).

HPLC System B t_R=14.4' >95%

Mass spec (FAB) m/e=508 $[M+H]^+$

EXAMPLE 108



108a Methyl (2R,5S)-1-*tert*-butyloxycarbonyl-5-phenyl-pyrrolidine-2-carboxylate.

This was prepared from **67b** on a 1.0 mmol scale following the method described for **104a**. The product was used without purification, assuming a yield of 100%.

108b Methyl (3R)-2-{(2R,5S)-1-*tert*-butyloxycarbonyl-5-phenyl-pyrrolidine-2-methyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **108a** and **26a** on a 1.0 mmol scale following the method described for **31a**. The intermediate aldehyde was isolated in 58% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v). The product was

isolated in 50% yield (based on a 0.58 mmol scale for the second part of the preparation) after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).

108c Methyl (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-methyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **108b** and **48a** on a 0.29 mmol scale following the method described for **1d**. The starting material **107a** was deprotected prior to coupling by treatment with 4*N* HCl in dioxan for 90 min. The product was isolated in 93% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

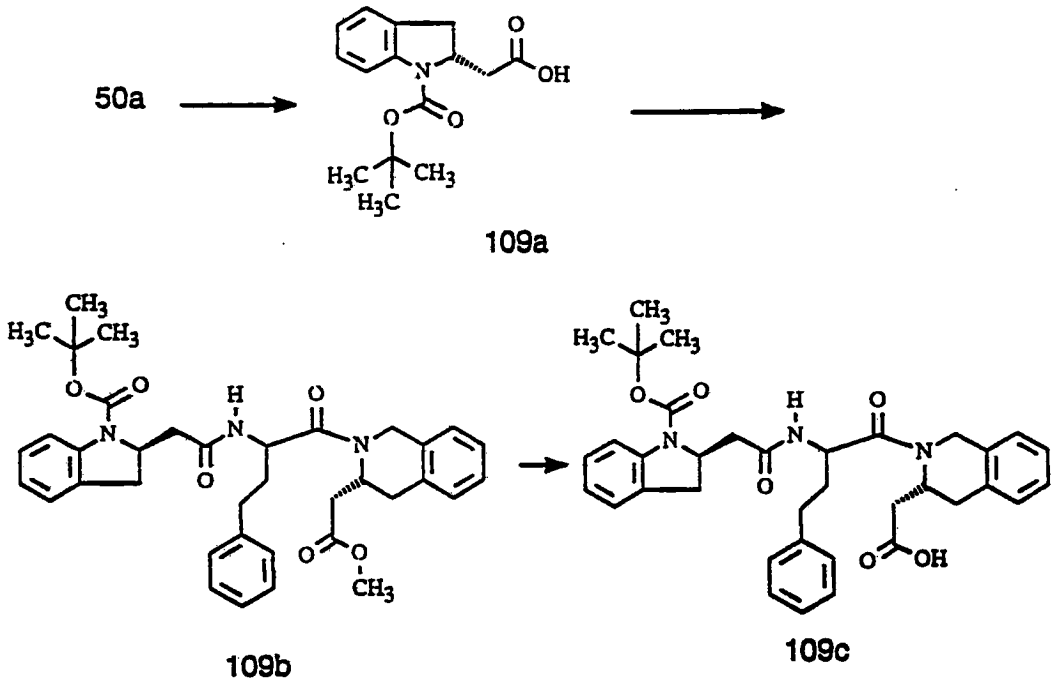
108d (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-methyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **108c** on a 0.27 mmol scale following the method described for **1f**. The product was isolated in 71% yield (111 mg) after flash chromatography on silica gel (eluant $CHCl_3$:MeOH:AcOH 100:3:2 v/v/v).

HPLC System A t_R=18.2' >99%

Mass spec (FAB) m/e=582 $[M+H]^+$

EXAMPLE 109



109a (2R)-1-*tert*-Butyloxycarbonyl-2.3-dihydroindole-2-acetic acid.

This was prepared from **50a** on a 0.25 mmol scale following the method described for **1f**. The product was used without further purification. assuming a yield of 100%.

109b Methyl (3R)-2-{(2S)-2-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-acetylamino)-4-phenylbutanoyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **13a** and **109a** on a 0.25 mmol scale following the method described for **32d**. The product was isolated in 90% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 25:75:2 v/v/v).

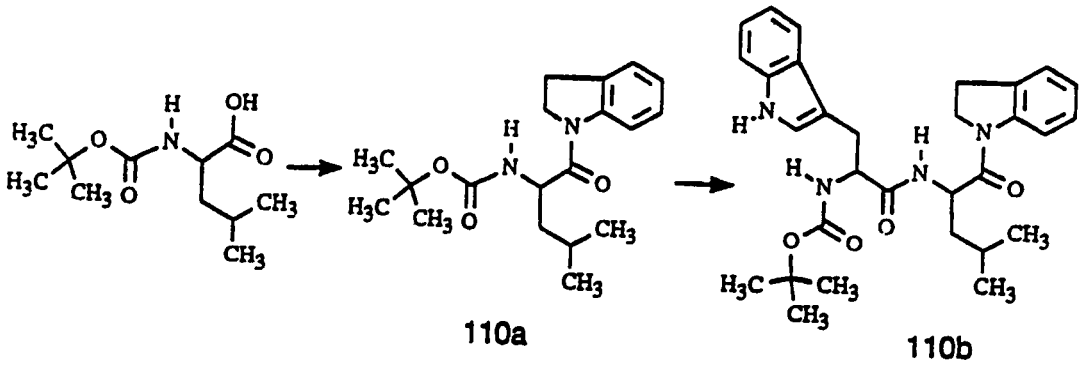
109c (3R)-2-{(2S)-2-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-acetylamino)-4-phenylbutanoyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **109b** on a 0.22 mmol scale following the method described for **1f**. The product was isolated in 80% yield (109 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 40:60:2 v/v/v).

HPLC System B t_R=15.2' >98%

Mass spec (FAB) m/e=612 $[M+H]^+$

EXAMPLE 110



110a 110b

110a 1-{*tert*-Butyloxycarbonyl-leucyl}-2,3-dihydroindole.

To an ice-cold stirred solution of BOC-Leu (4.62 g, 20 mmol) and pentafluorophenol (4.42 g, 24 mmol) in CH_2Cl_2 (100 mL) was added WSCD.HCl (7.65 g, 40 mmol). The mixture was stirred at 0°C for 1 hr., then indoline (4.0 mL, 36 mmol) and 4-dimethylaminopyridine were added and the mixture was stirred at room temperature for 4 days then concentrated *in vacuo*. The residue was partitioned between EtOAc and 0.3*M* $KHSO_4$, and the organic phase was washed with 0.3*M* $KHSO_4$, H_2O and brine, filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:pet. ether 10:90 v/v) to give the title product (3.41 g, 51%).

110b 1-{*tert*-Butyloxycarbonyl-tryptophanyl-leucyl}-2,3-dihydroindole.

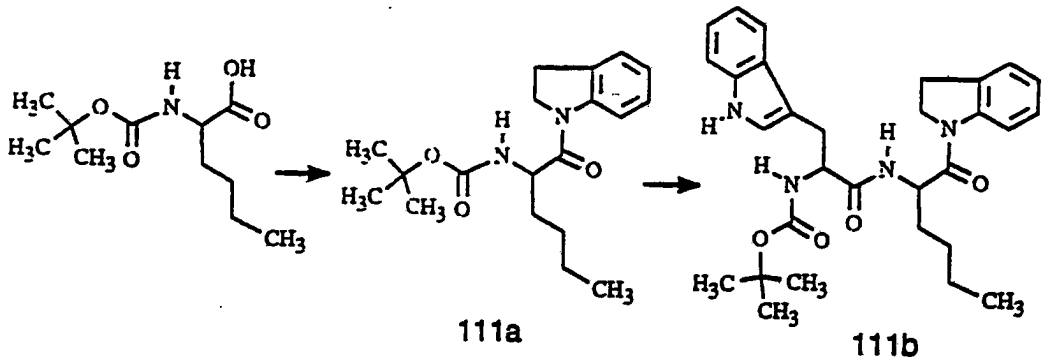
This was prepared from **110a** on a 1.08 mmol scale following the method described for **32d** using BOC-Trp instead of indoleacetic acid. The product was isolated in 79% yield (445 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 then 50:50 v/v).

HPLC System A t_R=17.5' >95%

AAA Peptide content=99%

Mass spec (FAB) m/e=519 $[M+H]^+$

EXAMPLE 111



111a 111b

111a 1-{(2S)-2-(*tert*-Butyloxycarbonylamino)-hexanoyl}-2,3-dihydroindole.

This was prepared from BOC-aminohexanoic acid on a 8.4 mmol scale following the method described for **110a.** The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

111b 1-{(2S)-2-(*tert*-Butyloxycarbonyl-tryptophanylamino)-hexanoyl}-2,3-dihydroindole.

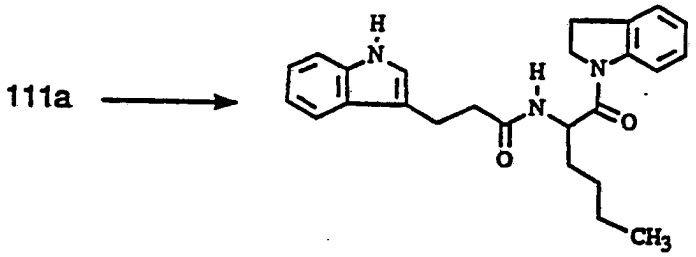
This was prepared from **111a** on a 0.88 mmol scale following the method described for **32d** using BOC-Trp instead of indoleacetic acid. The product was isolated in 66% yield (300 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 40:60:2 v/v/v).

HPLC System A t_R=14.8' >99%

AAA Peptide content=93%

Mass spec (FAB) m/e=519 $[M+H]^+$

EXAMPLE 112



112

112 1-{(2S)-2-(3-Indole-3-propanoylamino)-hexanoyl}-2,3-dihydroindole.

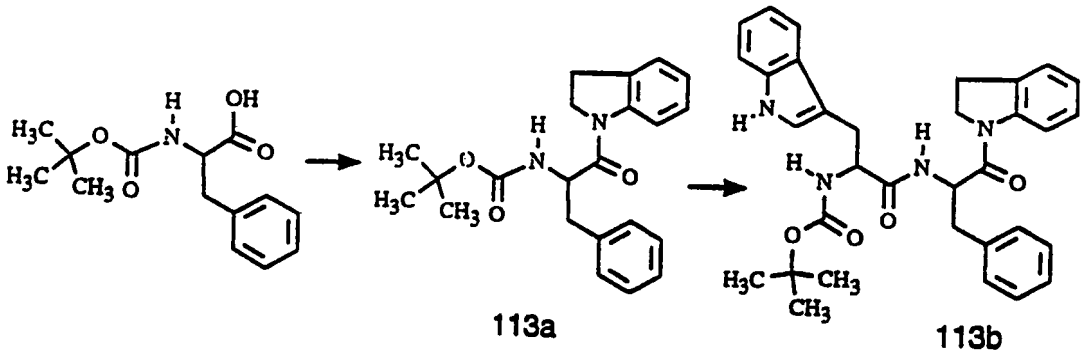
This was prepared from **111a** on a 0.63 mmol scale following the method described for **32d** using 3-indole-3-propanoic acid instead of indoleacetic acid. The product was isolated in 96% yield (244 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 30:70:2 then 40:60:2 v/v/v).

HPLC System A t_R=11.6' >95%

AAA Peptide content=88%

Mass spec (FAB) m/e=404 $[M+H]^+$

EXAMPLE 113



113a **113b**

113a 1-{*tert*-Butyloxycarbonyl-phenylalanyl}-2,3-dihydroindole.

This was prepared from BOC-Phe on a 0.75 mmol scale following the method described for **110a**. The product was isolated in 60% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).

113b 1-{*tert*-Butyloxycarbonyl-tryptophanyl-phenylalanyl}-2,3-dihydroindole.

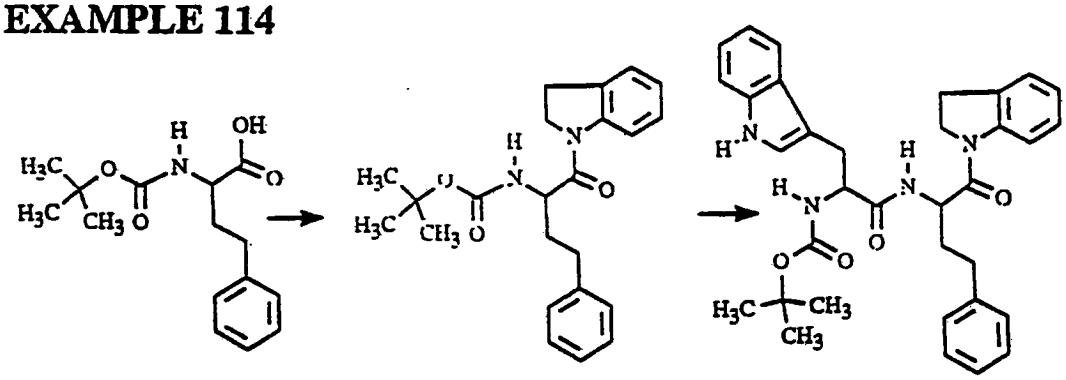
This was prepared from **113a** on a 0.45 mmol scale following the method described for **32d** using BOC-Trp instead of indoleacetic acid. The product was isolated in 61% yield (152 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether 50:50 v/v).

HPLC System A t_R=18.9' >95%

AAA Peptide content=90%

Mass spec (FAB) m/e=553 $[M+H]^+$

EXAMPLE 114



114a 114b

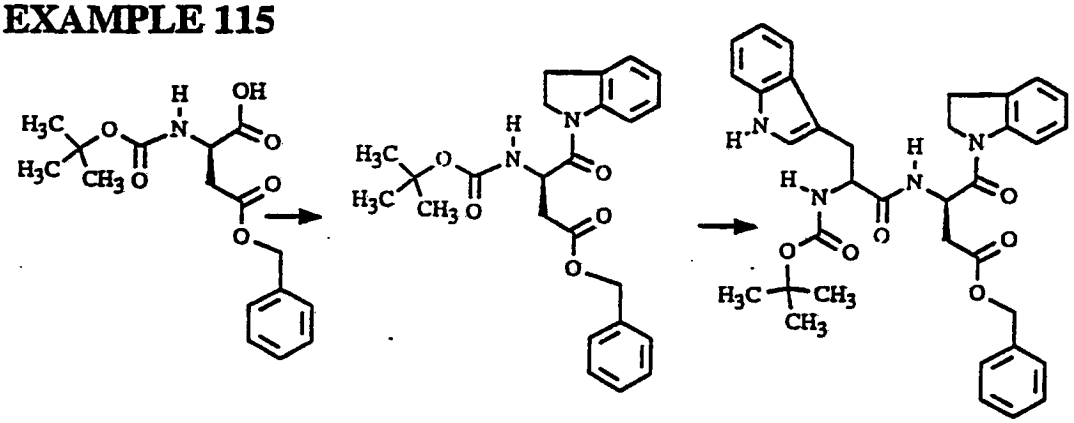
114a 1-{(2S)-2-(*tert*-Butyloxycarbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole.

This was prepared from BOC-homophenylalanine on a 2.25 mmol scale following the method described for 110a. The product was isolated in 64% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 18:82 v/v).

114b 1-{(2S)-2-(*tert*-Butyloxycarbonyl-tryptophanylamino)-4-phenylbutanoyl}-2,3-dihydroindole.

This was prepared from 114a on a 0.48 mmol scale following the method described for 32d using BOC-Trp instead of indoleacetic acid. The product was isolated in 73% yield (197 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether 50:50 v/v).
HPLC System A t_R=20.2' >98%
AAA Peptide content=100%
Mass spec (FAB) m/e=567 $[M+H]^+$

EXAMPLE 115



115a 115b

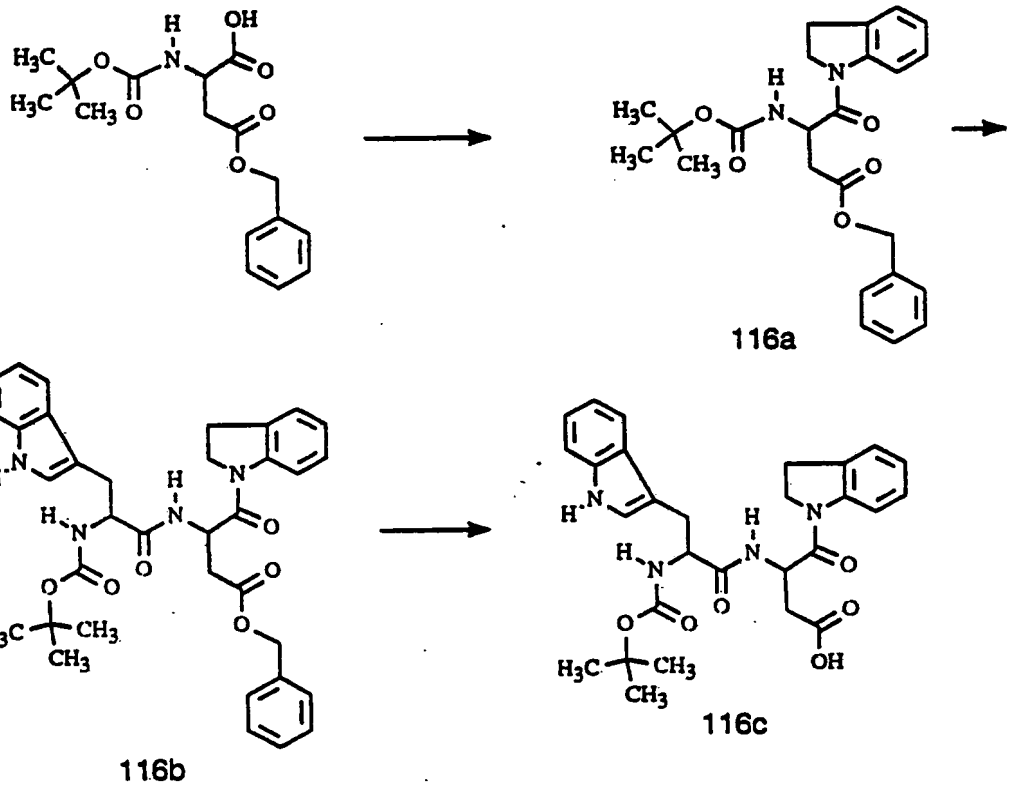
115a 1-{*tert*-Butyloxycarbonyl-(β-O-benzyl)-D-aspartyl}-2.3-dihydroindole.

This was prepared from BOC-D-Asp(OBzl)OH on a 4.0 mmol scale following the method described for **110a.** The product was isolated in 72% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).

115b 1-{*tert*-Butyloxycarbonyl-tryptophanyl-(β-O-benzyl)-D-aspartyl}-2.3-dihydroindole.

This was prepared from **115a** on a 1.18 mmol scale following the method described for **32d** using BOC-Trp instead of indoleacetic acid. The product was isolated in 45% yield (325 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).
HPLC System A t_R=17.2' >99%
AAA Peptide content=91%
Mass spec (FAB) m/e=611 $[M+H]^+$

EXAMPLE 116



116a 1-{*tert*-Butyloxycarbonyl-(β-O-benzyl)-aspartyl}-2,3-dihydroindole.

This was prepared from BOC-Asp(OBzl)OH on a 4.0 mmol scale following the method described for **110a**. The product was isolated in 57% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).

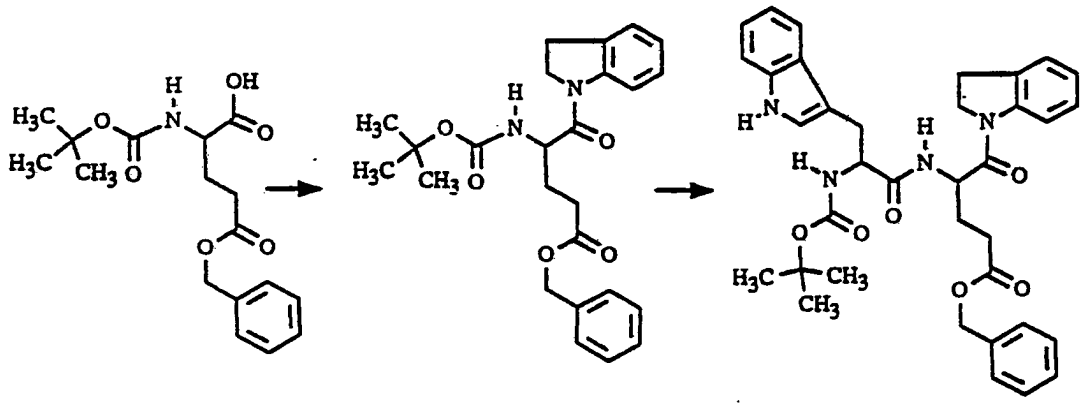
116b 1-{*tert*-Butyloxycarbonyl-tryptophanyl-(β-O-benzyl)-aspartyl}-2,3-dihydroindole.

This was prepared from **116a** on a 1.18 mmol scale following the method described for **32d** using BOC-Trp instead of indoleacetic acid. The product was isolated in 55% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

116c 1-{*tert*-Butyloxycarbonyl-tryptophanyl-aspartyl}-2,3-dihydroindole.

This was prepared from **116b** on a 0.32 mmol scale following the method described for **1f**. The product was isolated in 73% yield (122 mg) without purification.
HPLC System A t_R=8.5' >99%
AAA Peptide content=91%
Mass spec (FAB) m/e=521 $[M+H]^+$

EXAMPLE 117



117a 117b

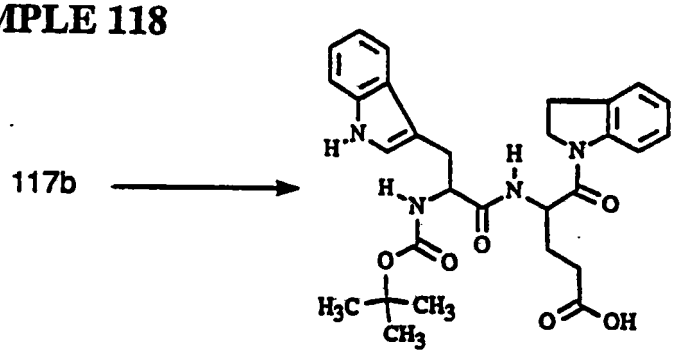
117a 1-{*tert*-Butyloxycarbonyl-(γ-O-benzyl)-glutamyl}-2,3-dihydroindole.

This was prepared from BOC-Glu(OBzl)OH on a 4.0 mmol scale following the method described for **110a**. The product was isolated in 45% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).

117b 1-{*tert*-Butyloxycarbonyl-tryptophanyl-(γ-O-benzyl)-glutamyl}-2,3-dihydroindole.

This was prepared from 117a on a 1.18 mmol scale following the method described for 32d using BOC-Trp instead of indoleacetic acid. The product was isolated in 59% yield (437 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).
HPLC System A t_R=17.9' >99%
AAA Peptide content=94%
Mass spec (FAB) m/e=625 $[M+H]^+$

EXAMPLE 118

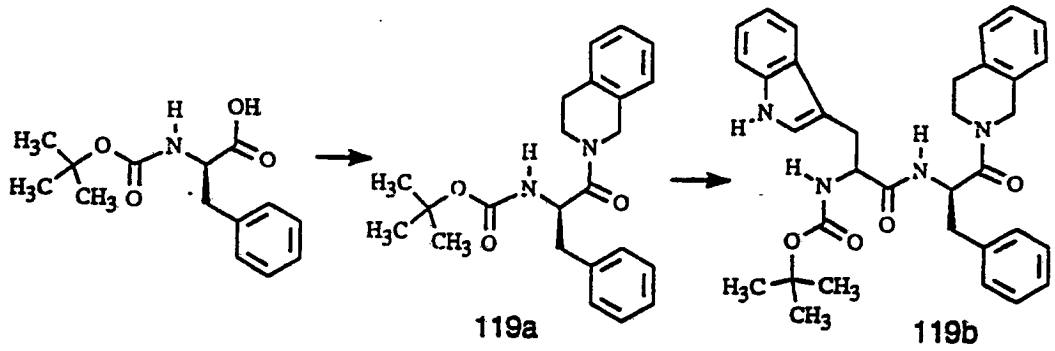


118

118 1-{*tert*-Butyloxycarbonyl-tryptophanyl-glutamyl}-2,3-dihydroindole.

This was prepared from 117b on a 0.35 mmol scale following the method described for 1f. The product was isolated in 70% yield (132 mg) after flash chromatography on silica gel (eluant EtOAc then EtOAc:AcOH 100:1 v/v).
HPLC System A t_R=9.1' >98%
AAA Peptide content=87%
Mass spec (FAB) m/e=535 $[M+H]^+$

EXAMPLE 119



119a 2-{*tert*-Butyloxycarbonyl-D-phenylalanyl}-1,2,3,4-tetrahydroisoquinoline.

This was prepared from BOC-D-Phe and tetrahydroisoquinoline on a 0.75 mmol scale following the method described for **110a**. The product was isolated in 77% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

119b 2-{*tert*-Butyloxycarbonyl-tryptophanyl-D-phenylalanyl}-1,2,3,4-tetrahydroisoquinoline.

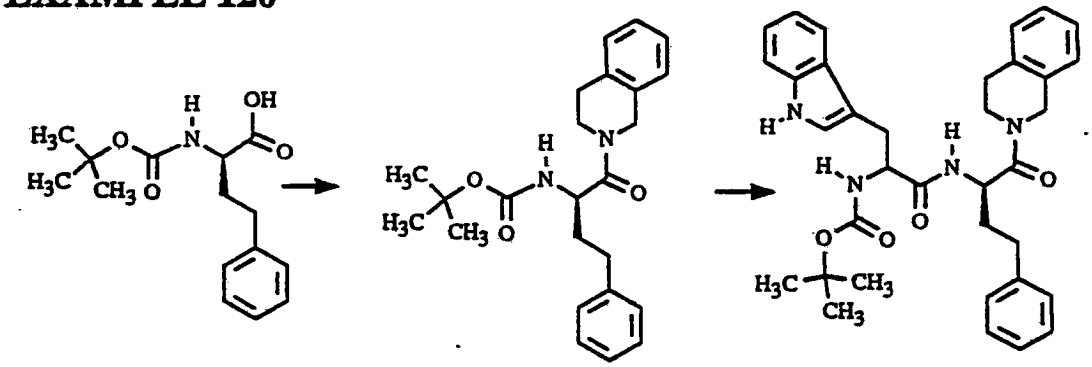
This was prepared from **119a** on a 0.58 mmol scale following the method described for **32d** using BOC-Trp instead of indoleacetic acid. The product was isolated in 72% yield (237 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether 50:50 v/v).

HPLC System A t_R=18.3' >98%

AAA Peptide content=84%

Mass spec (FAB) m/e=567 $[M+H]^+$

EXAMPLE 120



120a **2-{(2R)-2-(*tert*-Butyloxycarbonylamino)-4-phenylbutanoyl}-1,2,3,4-tetrahydroisoquinoline.**

This was prepared from BOC-D-homophenylalanine and tetrahydroisoquinoline on a 0.72 mmol scale following the method described for **110a**. The product was isolated in 85% yield and used without further purification.

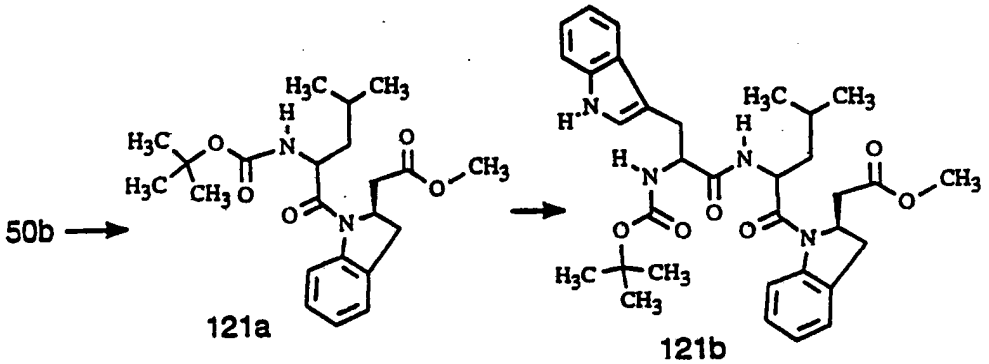
120b **2-{(2R)-2-(*tert*-Butyloxycarbonyl-tryptophanylamino)-4-phenylbutanoyl}-1,2,3,4-tetrahydroisoquinoline.**

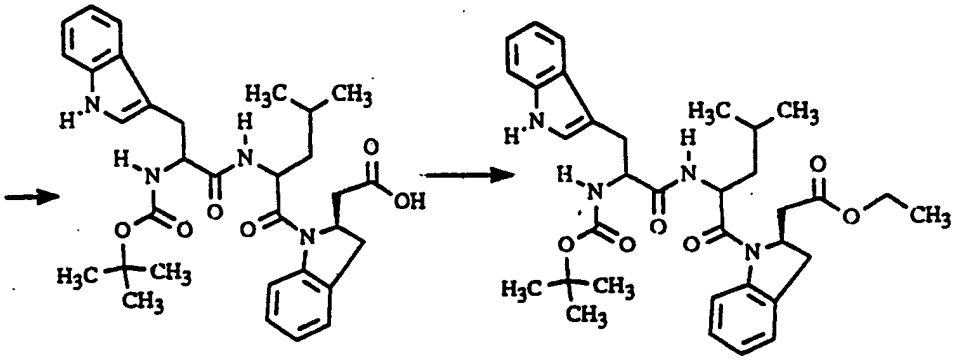
This was prepared from **120a** on a 0.67 mmol scale following the method described for **32d** using BOC-Trp instead of indoleacetic acid. The product was isolated in 69% yield (270 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 50:50:2 v/v/v).

HPLC System A t_R=16.3' >99%

AAA Peptide content=97%

EXAMPLE 121





121a Methyl (2R)-1-{*tert*-butyloxycarbonyl-leucyl}-2.3-dihydroindole-2-acetate.

This was prepared from BOC-Leu and **50b** on a 0.6 mmol scale following the method described for 1d. The product was isolated in 38% yield after flash chromatography on silica gel (eluant EtOAc:hexane 14:86 v/v).

121b Methyl (2R)-1-{*tert*-butyloxycarbonyl-tryptophanyl-leucyl}-2.3-dihydroindole-2-acetate.

This was prepared from **121a** on a 0.67 mmol scale following the method described for **32d** using BOC-Trp instead of indoleacetic acid. The product was isolated in 94% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 35:65:2 v/v/v).

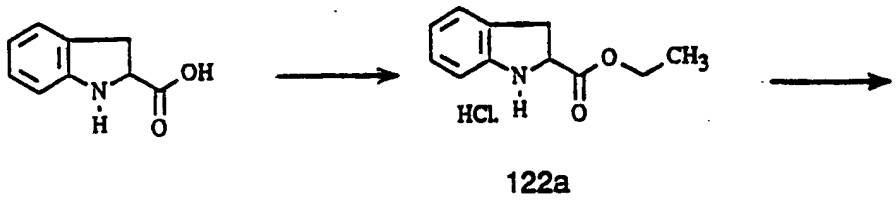
121c (2R)-1-{*tert*-Butyloxycarbonyl-tryptophanyl-leucyl}-2,3-dihydroindole-2-acetic acid.

This was prepared from **121b** on a 0.16 mmol scale following the method described for **1f**. The product was isolated in 85% yield and used without further purification.

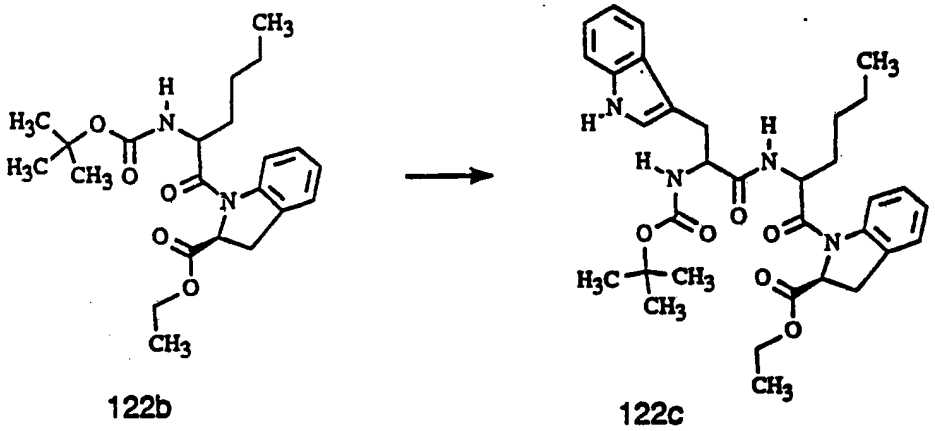
121d Ethyl (2R)-1-{*tert*-butyloxycarbonyl-tryptophanyl-leucyl}-2,3-dihydroindole-2-acetate.

This was prepared from **121c** on a 0.12 mmol scale following the method described for **104a** using EtOH instead of MeOH. The product was isolated in 82% yield (60 mg) after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).
HPLC System B t_R=17.3' >98%
AAA Peptide content=86%
Mass spec (FAB) m/e=605 $[M+H]^+$

EXAMPLE 122



122a



122b 122c

122a Ethyl (2RS)-2,3-dihydroindole-2-carboxylate hydrochloride.

This was prepared from (RS)-indoline-2-carboxylic acid on a 5.0 mmol scale following the method described for **26a** using EtOH instead of MeOH. The product was isolated in 96% yield and used without further purification.

122b Ethyl (2RS)-1-{(2S)-2-(*tert*-butyloxycarbonylamino)-hexanoyl}-2,3-dihydroindole-2-carboxylate.

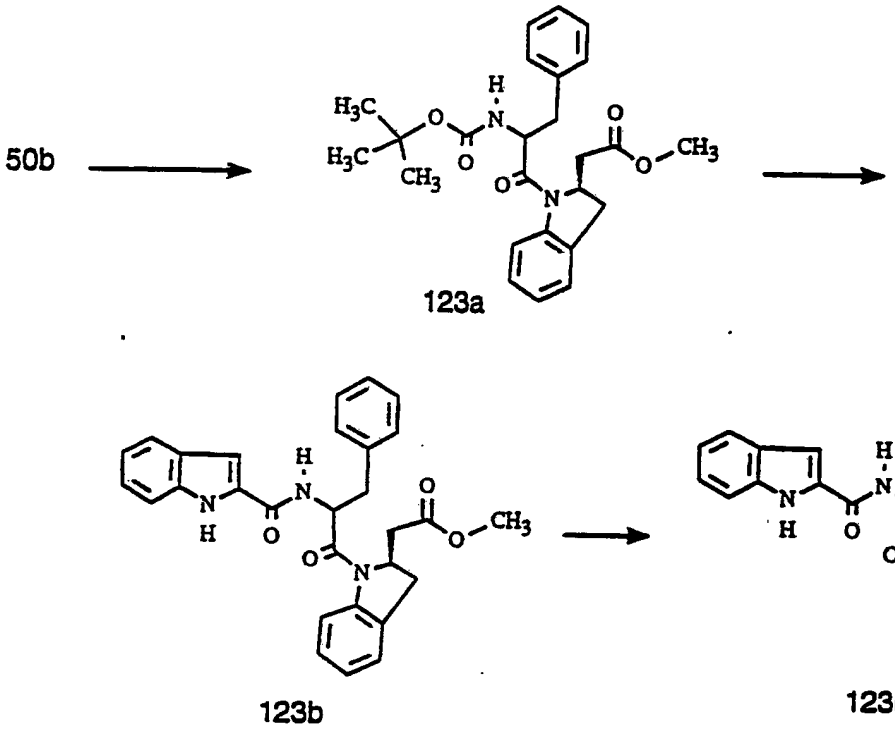
This was prepared from **122a** and BOC-aminohexanoic acid on a 6.0 mmol scale following the method described for **1d**. The product was isolated in 62% yield after flash chromatography on silica gel (eluant EtOAc:hexane 25:75 v/v).

122c Ethyl (2S)-1-{(2S)-2-(*tert*-butyloxycarbonyl-tryptophanylamino)-hexanoyl}-2,3-dihydroindole-2-carboxylate.

This was prepared from **122b** on a 1.88 mmol scale following the method described for **32d** using BOC-Trp instead of indoleacetic acid. The product was isolated in 20% yield (220 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 28:72:2 v/v/v). The (2R)-indoline epimer was separated at this stage (43% yield).

HPLC System B t_R=16.6' >98%
AAA Peptide content=90%
Mass spec (FAB) m/e=591 $[M+H]^+$

EXAMPLE 123



123a Methyl (2R)-1-{*tert*-butyloxycarbonyl-phenylalanyl}-2,3-dihydroindole-2-acetate.

This was prepared from BOC-Phe and **50b** on a 0.52 mmol scale following the method described for **1d**. The product was isolated in 45% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 15:85 v/v).

123b Methyl (2R)-1-{indole-2-carbonyl-phenylalanyl}-2,3-dihydroindole-2-acetate.

The compound **123a** was deprotected on a 0.23 mmol scale following the method described for **1c** to give methyl (2R)-1-phenylalanyl-2,3-dihydroindole-2-acetate hydrochloride which was then treated with indole-2-carbonyl chloride in the following manner.

To a stirred suspension of indole-2-carboxylic acid dicyclohexylamine salt (103 mg, 0.30 mmol) in CH_2Cl_2 (15 mL) was added pyridine (32.3 µL, 0.4 mmol) and then $SOCl_2$

(180 µL of 2*M* solution in CH_2Cl_2, 0.36 mmol). The mixture was stirred at room temperature for 1 min., then the methyl (2R)-1-phenylalanyl-2,3-dihydroindole-2-acetate hydrochloride and 4-dimethylaminopyridine ((25 mg, 0.21 mmol) were added. The mixture was stirred at room temperature for 2 hr. and then concentrated *in vacuo*. The residue was partitioned between EtOAc and H_2O, and the organic phase was washed with 10% $KHSO_4$, satd. $KHCO_3$ and brine, filtered (Whatman^R 1PS phase separator), and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v) to give the title compound (32 mg, 28%).

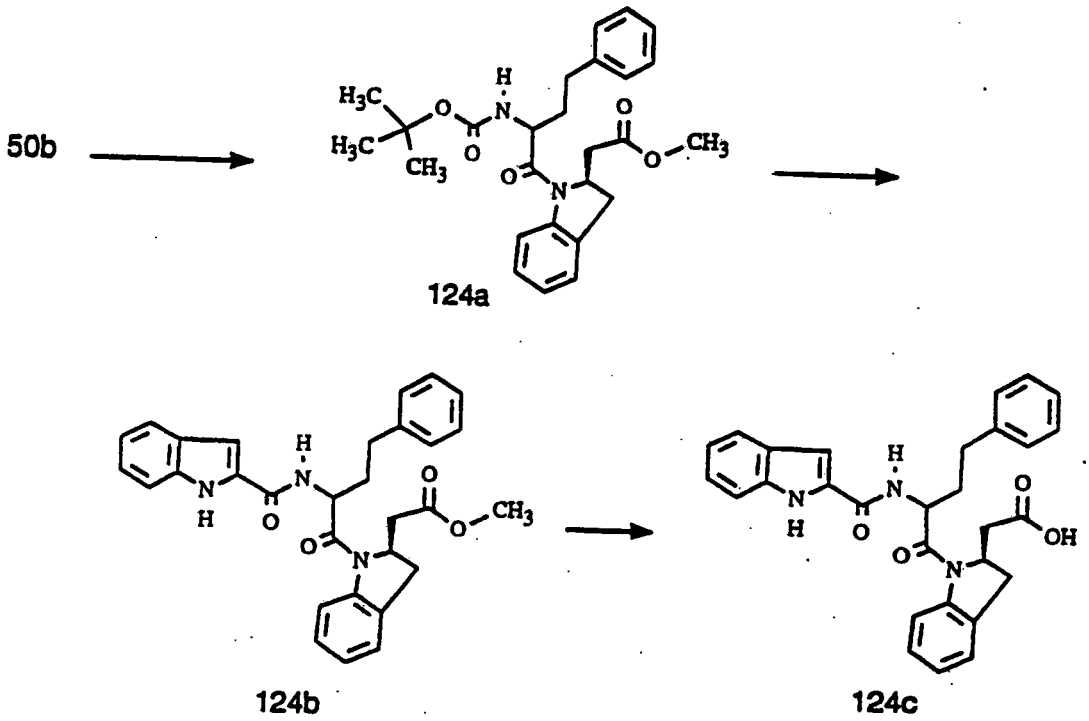
123c (2R)-1-{Indole-2-carbonyl-phenylalanyl}-2,3-dihydroindole-2-acetic acid.

This was prepared from **123b** on a 0.066 mmol scale following the method described for **1f**. The product was isolated in 90% yield (28 mg) without purification.

HPLC System B t_R=9.9' >90%

Mass spec (FAB) m/e=468 $[M+H]^+$

EXAMPLE 124



124a Methyl (2R)-1-{(2S)-2-(*tert*-butyloxycarbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetate.

This was prepared from BOC-homophenylalanine and racemic **50b** on a 5.0 mmol scale following the method described for **1d**. The product was isolated in 14% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 18:82 v/v) together with the (2R)-indoline epimer (isolated in 22% yield).

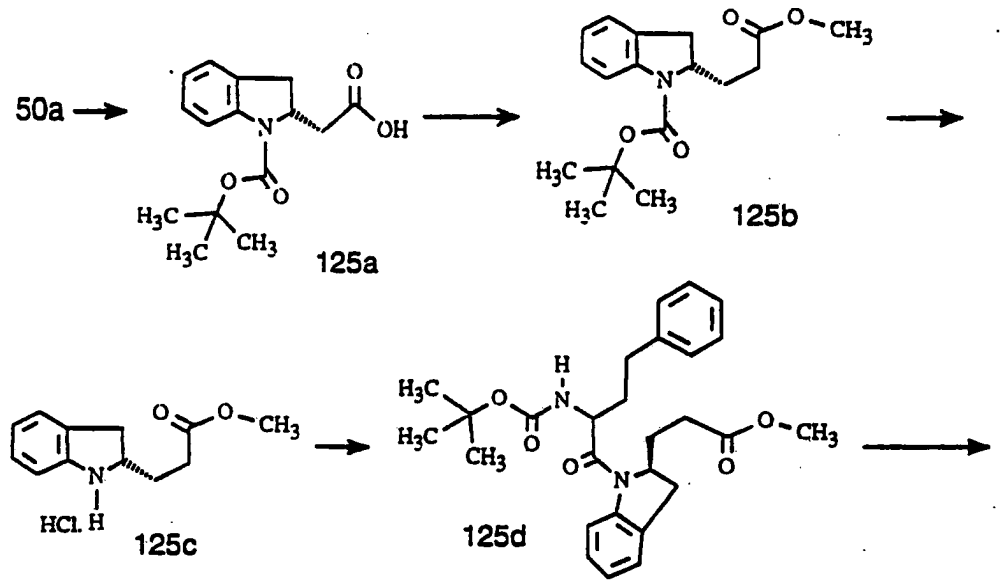
124b Methyl (2R)-1-{(2S)-2-(indole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetate.

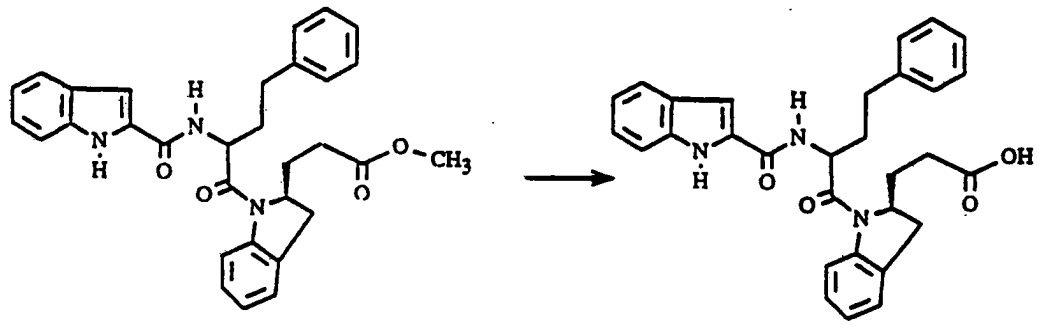
This was prepared from **124a** on a 0.34 mmol scale following the method described for **123b**. The semi-purified product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 35:65:2 v/v/v).

124c (2R)-1-{(2S)-2-(Indole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetic acid.

This was prepared from **124b** on a 0.34 mmol scale following the method described for **1f**. The product was isolated in 63% yield (196 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 45:55:2 v/v/v).
HPLC System A t_R=14.8' >95%
Mass spec (FAB) m/e=482 $[M+H]^+$

EXAMPLE 125





125a (2R)-1-*tert*-Butyloxycarbonyl-2.3-dihydroindole-2-acetic acid.

This was prepared from **50a** on a 3.4 mmol scale following the method described for **1f**. The product was used without purification. assuming a yield of 100%.

125b Methyl 3-{(2R)-1-*tert*-butyloxycarbonyl-2.3-dihydroindole-2-yl}-propanoate.

This was prepared from **125a** on a 3.4 mmol scale following the method described for **1b**. The product was isolated in 44% yield after flash chromatography on silica gel (eluant EtOAc:hexane 12:88 v/v).

125c Methyl 3-{(2R)-2.3-dihydroindole-2-yl}-propanoate hydrochloride.

This was prepared from **125b** on a 1.0 mmol scale following the method described for **1c**. The product was used without purification. assuming a yield of 100%.

125d Methyl 3-{(2R)-1-{(2S)-2-(*tert*-butyloxycarbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-yl}-propanoate.

This was prepared from 125c and BOC-homophenylalanine on a 1.0 mmol scale following the method described for 1d. The product was isolated in 64% yield after flash chromatography on silica gel (eluant EtOAc:hexane 20:80 v/v).

125e Methyl 3-{(2R)-1-{(2S)-2-(indole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-yl}-propanoate.

This was prepared from 125d on a 0.43 mmol scale following the method described for 123b. The product was isolated in 41% yield after flash chromatography on silica gel (eluant EtOAc:hexane 30:70 v/v).

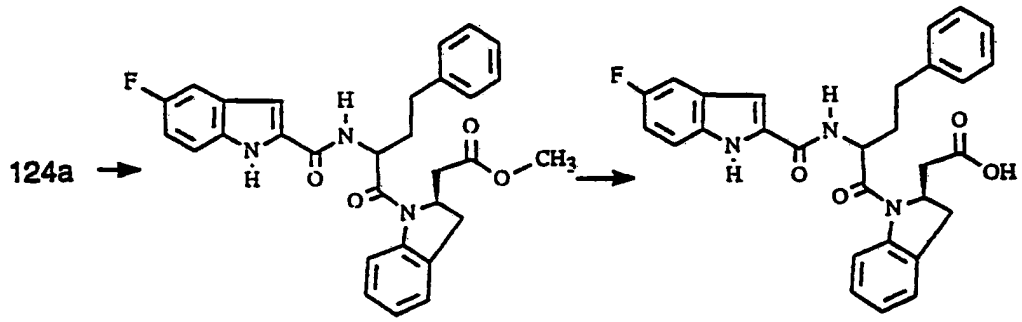
125f 3-{(2R)-1-{(2S)-2-(Indole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-yl}-propanoic acid.

This was prepared from 125e on a 0.18 mmol scale following the method described for 1f. The product was isolated in 56% yield (43 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 40:60:2 v/v/v).

HPLC System B t_R=11.2' >80%

Mass spec (FAB) m/e=518 $[M+H]^+$

EXAMPLE 126



126a 126b

126a Methyl (2R)-1-{(2S)-2-(5-fluoroindole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetate.

This was prepared from 124a and 5-fluoroindole-2-carboxylic acid on a 0.20 mmol scale following the method described for 123b. The product was isolated in 54% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

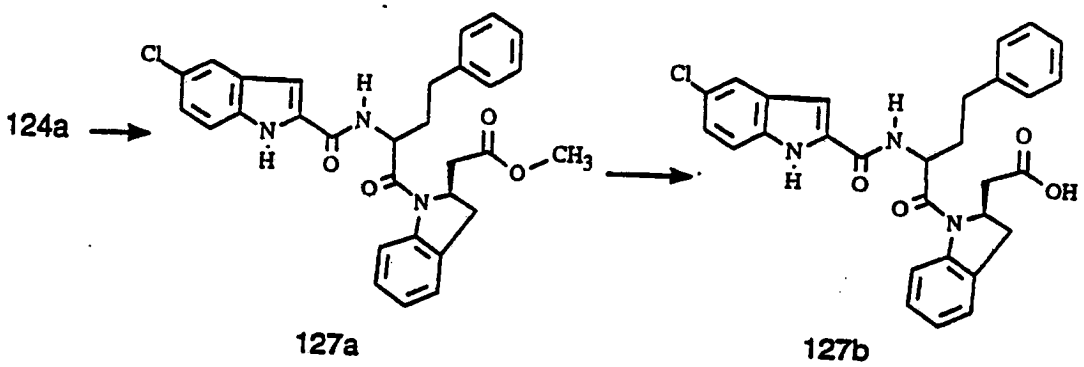
126b (2R)-1-{(2S)-2-(5-Fluoroindole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetic acid.

This was prepared from **126a** on a 0.11 mmol scale following the method described for **1f**. The product was isolated in 73% yield (39 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 45:55:2 v/v/v).

HPLC System A t_R=14.2' >95%

Mass spec (FAB) m/e=500 $[M+H]^+$

EXAMPLE 127



127a Methyl (2R)-1-{(2S)-2-(5-chloroindole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetic acid.

This was prepared from **124a** and 5-chloroindole-2-carboxylic acid on a 0.20 mmol scale following the method described for **123b**. The product was isolated in 52% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

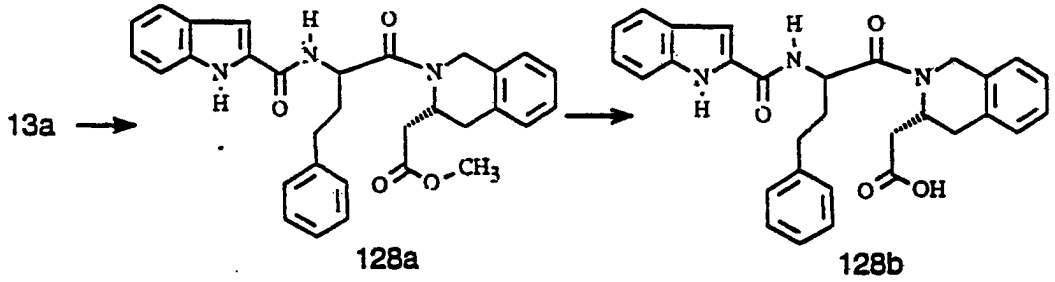
127b (2R)-1-{(2S)-2-(5-Chloroindole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetic acid.

This was prepared from **127a** on a 0.10 mmol scale following the method described for **1f**. The product was isolated in 78% yield (42 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 45:55:2 v/v/v).

HPLC System A t_R=16.0' >95%

Mass spec (FAB) m/e=511 $[M+H]^+$

EXAMPLE 128



128a Methyl (3R)-2-{(2S)-2-(indole-2-carbonylamino)-4-phenylbutanoyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **13a** on a 0.12 mmol scale following the method described for **123b**. The product was isolated in 68% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 35:65:2 v/v/v).

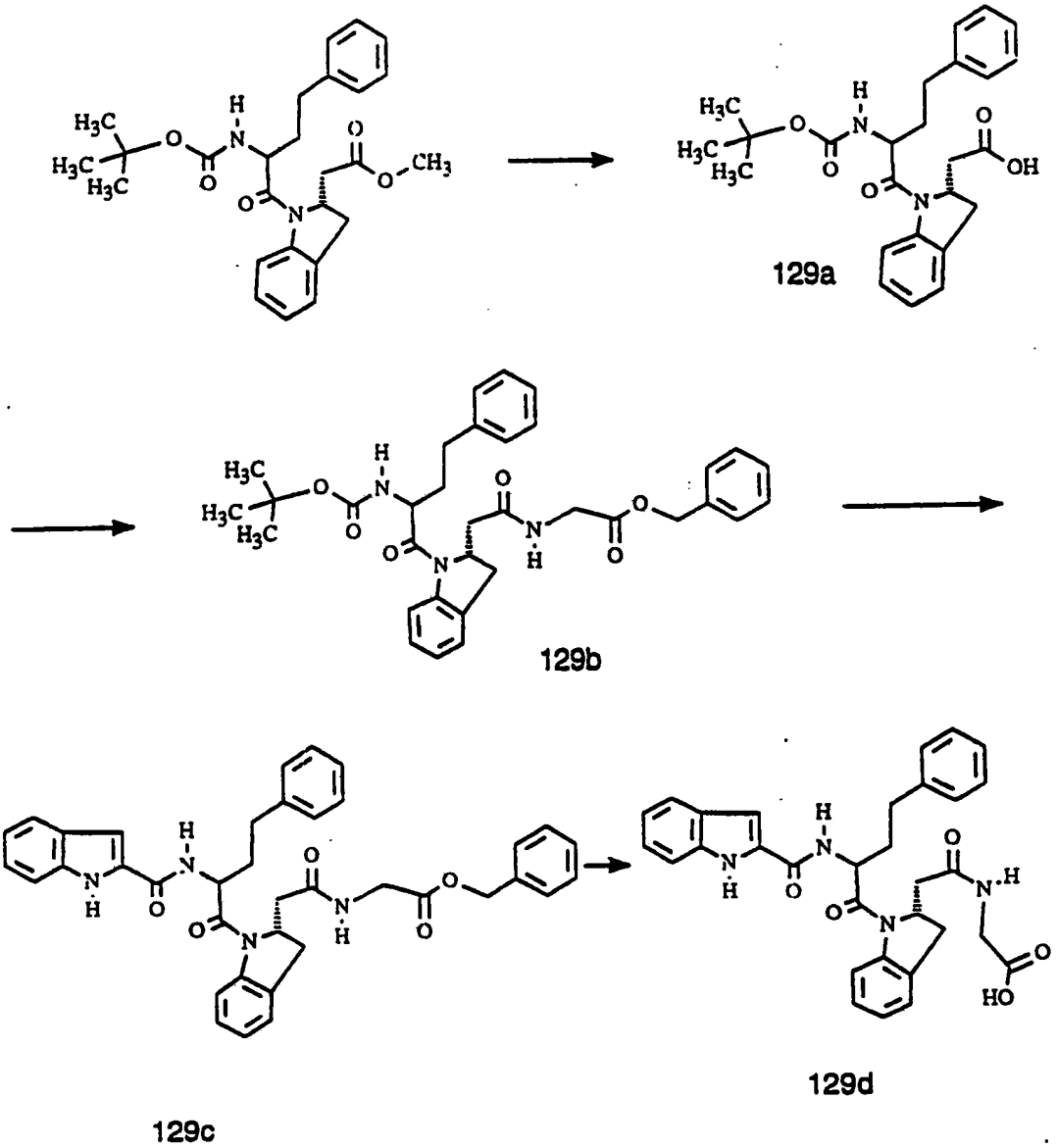
128b (3R)-2-{(2S)-2-(Indole-2-carbonylamino)-4-phenylbutanoyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **128a** on a 0.09 mmol scale following the method described for **1f**. The product was isolated in 66% yield (31 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 40:60:2 v/v/v).

HPLC System A t_R=14.8' >99%

Mass spec (FAB) m/e=496 $[M+H]^+$

EXAMPLE 129



129a (2S)-1-{(2S)-2-(*tert*-Butyloxycarbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetic acid.

This was prepared from the (2S)-indoline epimer of **124a** on a 0.68 mmol scale following the method described for **1f**. The product was used without purification, assuming a yield of 100%.

129b Benzyl N-{(2S)-1-{(2S)-2-(*tert*-butyloxycarbonylamino)-4-phenylbutanoyl}-2.3-dihydroindole-2-acetyl}-glycinate.

This was prepared from **129a** and GlyOBzl on a 0.68 mmol scale following the method described for **1d.** The product was isolated in 53% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

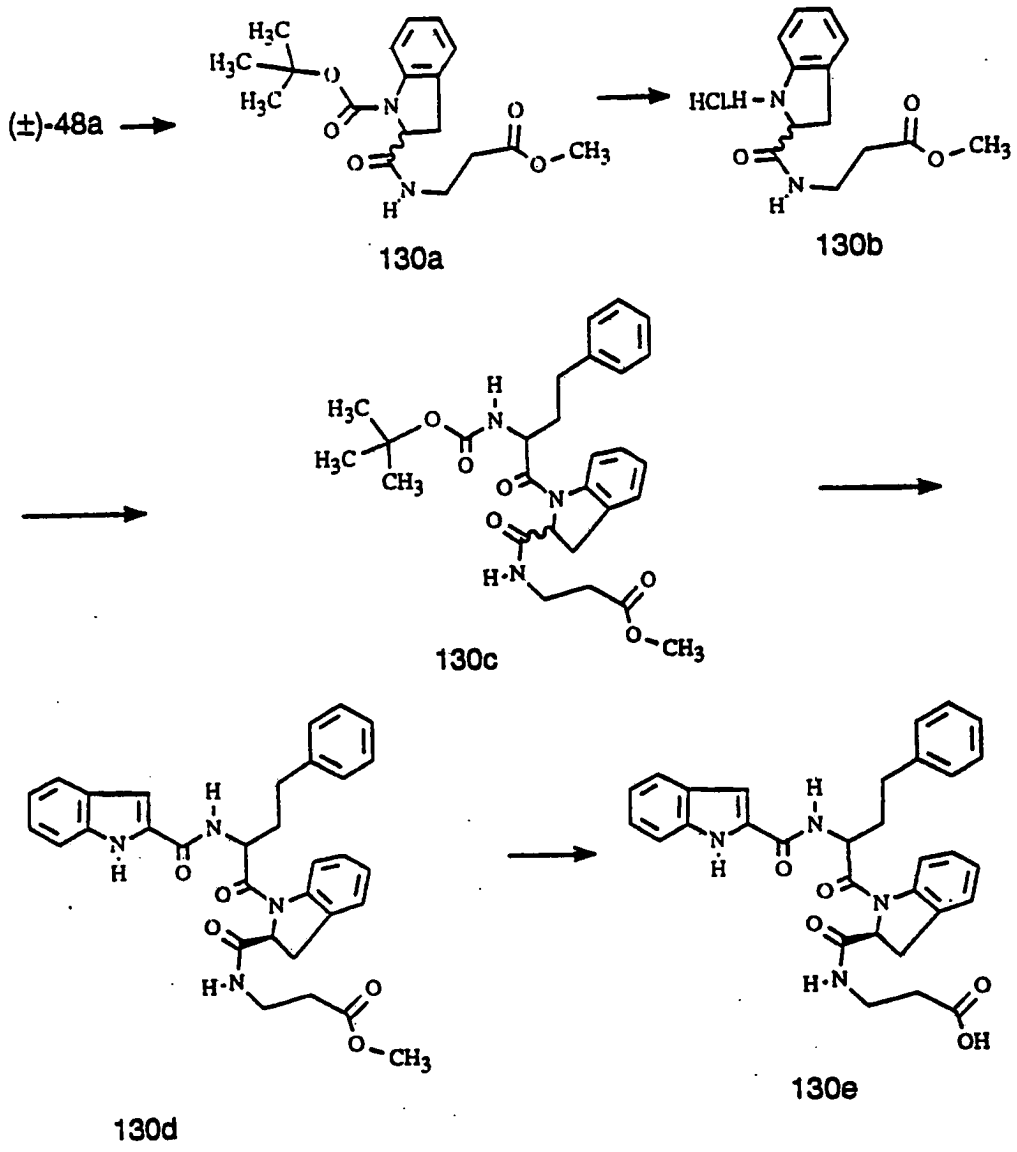
129c Benzyl N-{(2S)-1-{(2S)-2-(indole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetyl}-glycinate.

This was prepared from **129b** and on a 0.36 mmol scale following the method described for **123b.** The product was isolated in 45% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

129d N-{(2S)-1-{(2S)-2-(Indole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetyl}-glycine.

This was prepared from **129c** on a 0.16 mmol scale following the method described for **1f.** The product was isolated in 30% yield (26 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 90:10:2 v/v/v).
HPLC System A t_R=13.6' >95%
Mass spec (FAB) m/e=539 $[M+H]^+$

EXAMPLE 130



130a Methyl 3-{(2RS)-1-*tert*-butyloxycarbonyl-2.3-dihydroindole-2-carbonylamino}-propanoate.

This was prepared from racemic 48a and β-alanineOMe on a 1.8 mmol scale following the method described for 1d. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 50:50 v/v).

130b Methyl 3-{(2RS)-2,3-dihydroindole-2-carbonylamino}-propanoic acid hydrochloride.

This was prepared from 130a on a 1.2 mmol scale following the method described for 1c. The product was used without purification, assuming a yield of 100%.

130c Methyl 3-{(2RS)-1-{(2S)-2-(*tert*-butyloxycarbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-carbonylamino}-propanoic acid.

This was prepared from 130b and BOC-homophenylalanine on a 1.2 mmol scale following the method described for 1d. The product was isolated in 41% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 45:55 v/v).

130d Methyl 3-{(2S)-1-{(2S)-2-(indole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-carbonylamino}-propanoic acid.

This was prepared from 130c on a 0.49 mmol scale following the method described for 123b. The product was isolated in 28% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 55:45 v/v).

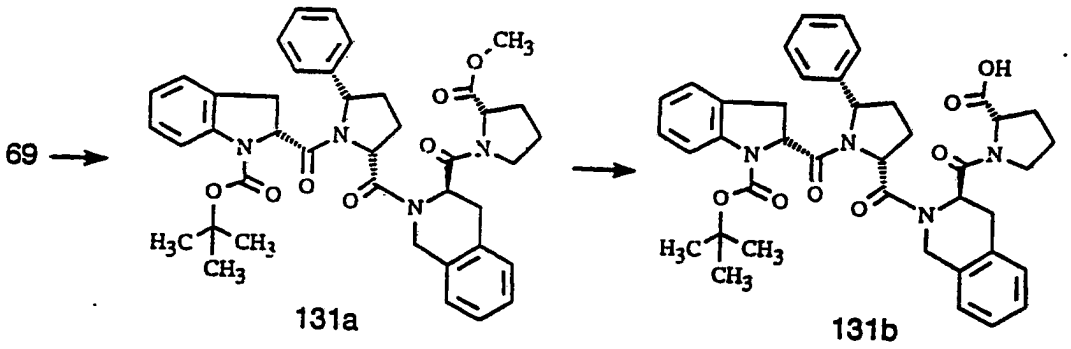
130e 3-{(2S)-1-{(2S)-2-(Indole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-carbonylamino}-propanoic acid.

This was prepared from 130d on a 0.09 mmol scale following the method described for 1f. The product was isolated in 97% yield (47 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 70:30:2 v/v/v).

HPLC System A t_R=12.6' >95%

Mass spec (FAB) m/e=539 $[M+H]^+$

EXAMPLE 131



131a Methyl N-{(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carbonyl}-prolinate.

This was prepared from 69 and ProOMe on a 0.30 mmol scale following the method described for **1d.** The product was isolated in 18% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 then 70:30 v/v).

R_f (EtOAc:hexane 70:30 v/v) 0.22

131b N-{(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carbonyl}-proline.

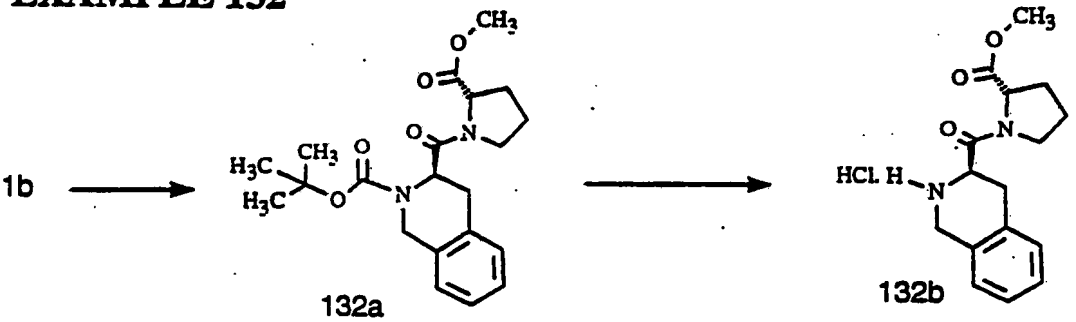
This was prepared from 131a on a 0.06 mmol scale following the method described for **1f.** The product was isolated in 49% yield (19 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

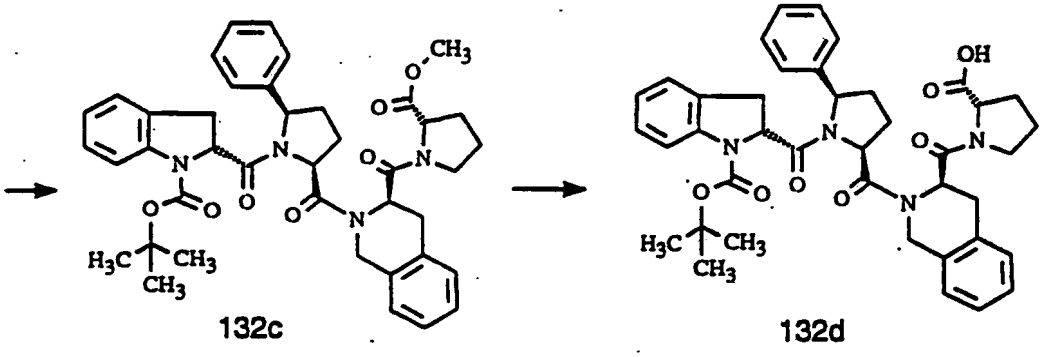
HPLC System A t_R=19.7' >98%

AAA Peptide content=73%

Mass spec (FAB) m/e=693 $[M+H]^+$

EXAMPLE 132





132a Methyl N-{(3R)-2-*tert*-butyloxycarbonyl-1.2.3.4-tetrahydroisoquinoline-3-carbonyl}-prolinate.

This was prepared from 1a and ProOMe on a 5.4 mmol scale following the method described for **1d**. The product was isolated in 68% yield after flash chromatography on silica gel (eluant EtOAc:hexane 70:30 v/v).

132b Methyl N-{(3R)-1,2.3,4-tetrahydroisoquinoline-3-carbonyl}-prolinate hydrochloride.

This was prepared from **132a** on a 0.13 mmol scale following the method described for **1c**. The product was used without purification assuming a yield of 100%.

132c Methyl N-{(3R)-2-{(2S.5R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2.3,4-tetrahydroisoquinoline-3-carbonyl}-prolinate.

This was prepared from **132b** and **88b** on a 0.13 mmol scale following the method described for **1d**. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 65:35 v/v).

R_f (EtOAc:hexane 80:20 v/v) 0.38

132d N-{(3R)-2-{(2S.5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1.2.3.4-tetrahydroisoquinoline-3-carbonyl}-proline.

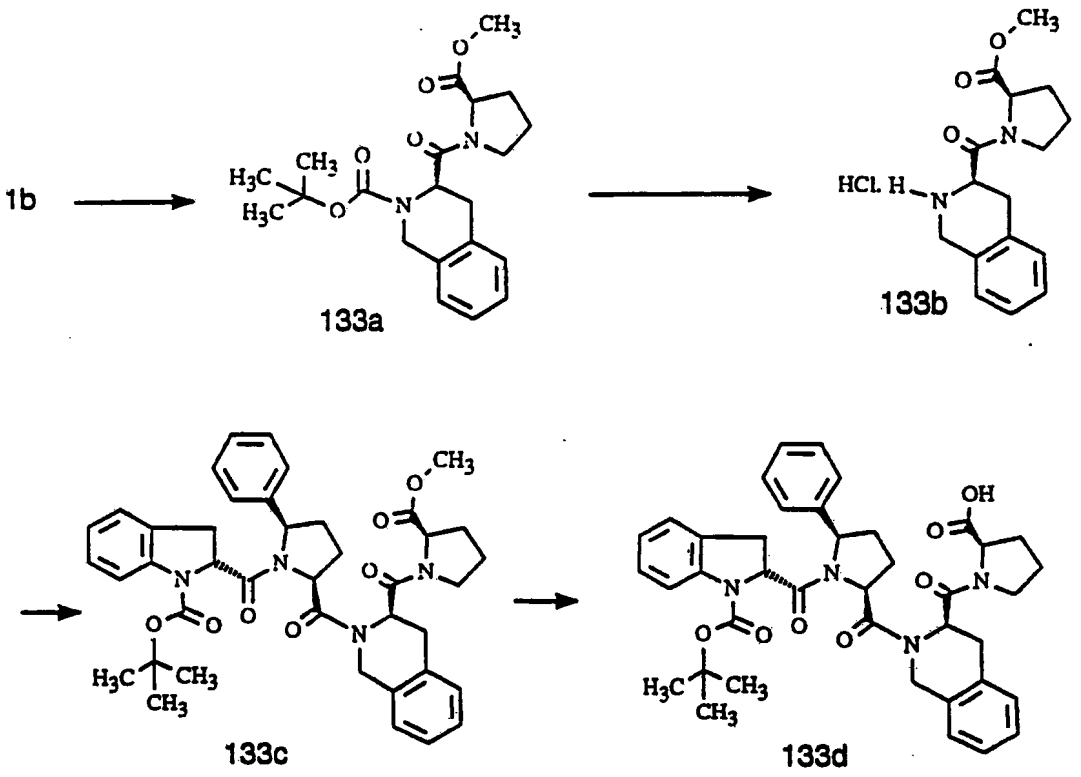
This was prepared from **132c** on a 0.13 mmol scale following the method described for **1f**. The product was isolated in 24% yield (21 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 90:10:2 v/v/v).

HPLC System A t_R=19.9' >95%

AAA Peptide content=81%

Mass spec (FAB) m/e=693 $[M+H]^+$

EXAMPLE 133



133a Methyl N-{(3R)-2-*tert*-butyloxycarbonyl-1.2.3.4-tetrahydroisoquinoline-3-carbonyl}-D-prolinate.

This was prepared from **1a** and D-ProOMe on a 0.56 mmol scale following the method described for **1d**. The product was isolated in 39% yield after flash chromatography on silica gel (eluant EtOAc:hexane 65:35 v/v).

R_f (EtOAc:hexane 70:30 v/v) 0.30

133b Methyl N-{(3R)-1.2.3.4-tetrahydroisoquinoline-3-carbonyl}-D-prolinate hydrochloride.

This was prepared from **133a** on a 0.13 mmol scale following the method described for **1c**. The product was used without purification assuming a yield of 100%.

133c Methyl N-{(3R)-2-{(2S,5R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carbonyl}-D-prolinate.

This was prepared from **133b** and **88b** on a 0.13 mmol scale following the method described for **1d**. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 65:35 v/v).

R_f (EtOAc:hexane 80:20 v/v) 0.30

133d N-{(3R)-2-{(2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carbonyl}-D-proline.

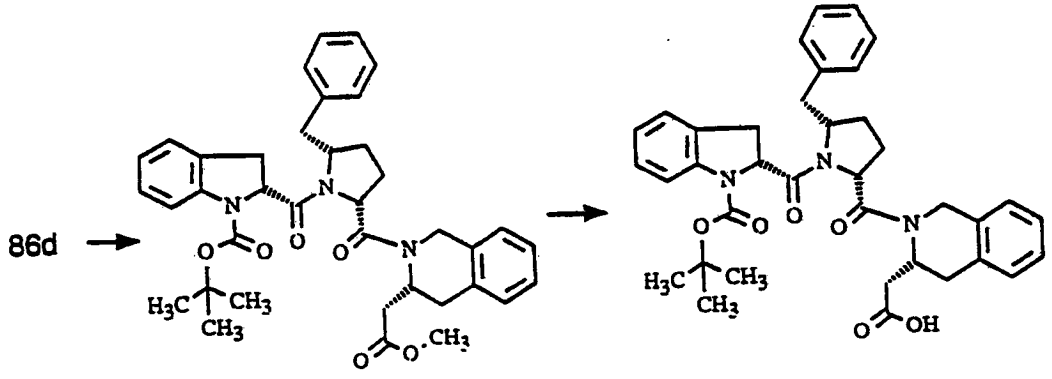
This was prepared from **133c** on a 0.13 mmol scale following the method described for **1f**. The product was isolated in 57% yield (51 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 95:5:2 v/v/v).

HPLC System A t_R=20.2' >95%

AAA Peptide content=91%

Mass spec (FAB) m/e=693 $[M+H]^+$

EXAMPLE 134



134a Methyl (3R)-2-{(2R.5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-5-benzyl-pyrrolidine-2-carbonyl}-1.2.3.4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **26a** and **86d** on a 0.5 mmol scale following the method described for **1d**. The product was isolated in 96% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

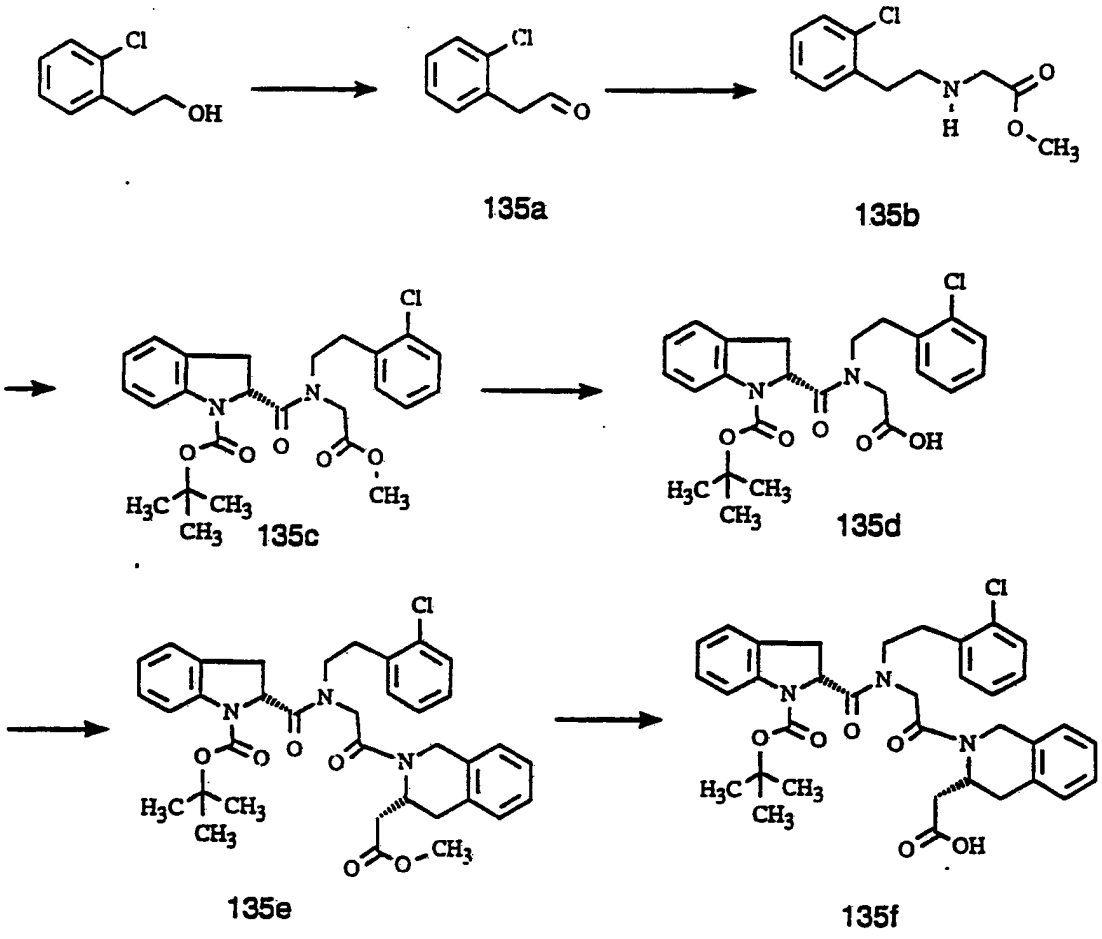
134b (3R)-2-{(2R.5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-5-benzyl-pyrrolidine-2-carbonyl}-1.2.3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **134a** on a 0.48 mmol scale following the method described for **1f**. The product was isolated in 51% yield (151 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 70:30:2 v/v/v).

HPLC System A t_R=14.4' >99%

Mass spec (FAB) m/e=510 $[M+H-BOC]^+$

EXAMPLE 135



135a 2-Chlorophenylacetaldehyde.

This was prepared from 2-chlorophenethyl alcohol on a 9.58 mmol scale following the method described for **99a**. The product was used without purification assuming a yield of 100%.

135b Methyl N-2-chlorophenethyl-glycinate.

This was prepared from **135a** on a 9.58 mmol scale following the method described for **42a**. The product was isolated in 8% yield after flash chromatography on silica gel (eluant EtOAc:hexane 80:20 v/v).

R_f (EtOAc:hexane 80:20 v/v) 0.12

^1H NMR δ 2.84-2.88 (4H,m): 3.40 (2H,s); 3.66 (3H,s); 7.06-7.29 (4H,m)

135c Methyl N-2-chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.

This was prepared from **135b** and **48a** on a 0.68 mmol scale following the method described for **1d**. The product was isolated in 76% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

R_f (EtOAc:hexane 40:60 v/v) 0.26

135d N-2-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from **135c** on a 0.52 mmol scale following the method described for **1f**. The product was isolated in 78% yield and used without further purification.

135e Methyl (3R)-2-{N-2-chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **135d** and **1c** on a 0.20 mmol scale following the method described for **1d**. The product was isolated in 58% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R_f (EtOAc:hexane 50:50 v/v) 0.25

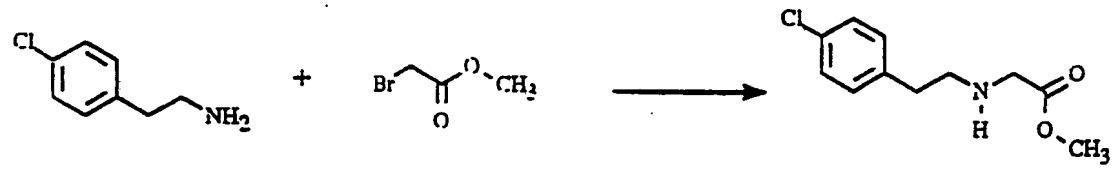
135f (3R)-2-{N-2-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **135e** on a 0.12 mmol scale following the method described for **1f**. The product was isolated in 50% yield (38 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 55:45:2 v/v/v).

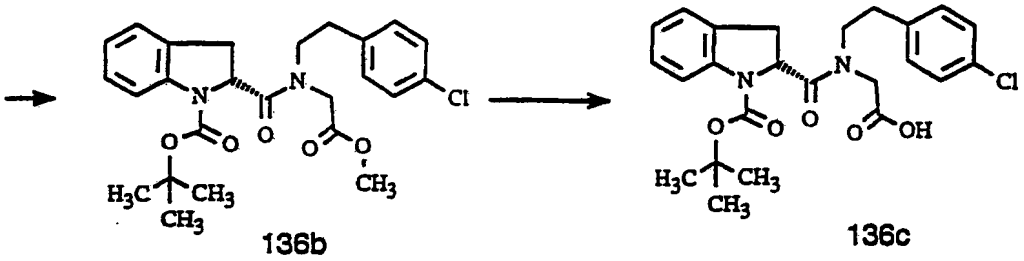
HPLC System A t_R=22.3' >90%

Mass spec (FAB) m/e=632 $[M+H]^+$

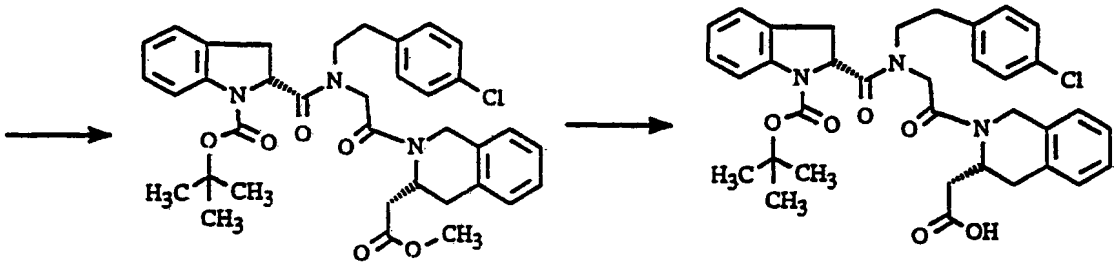
EXAMPLE 136



136a



136b 136c



136d 136e

136a Methyl N-4-chlorophenethyl-glycinate.

This was prepared from 2-chlorophenethylamine on a 6.43 mmol scale following the method described for **32a**. The product was isolated in 94% yield and used without purification.

136b Methyl N-4-chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.

This was prepared from **136a** and **48a** on a 1.7 mmol scale following the method described for **1d**. The product was isolated in 84% yield after flash chromatography on silica gel (eluant EtOAc:hexane 45:55 v/v).

R_f (EtOAc:hexane 50:50 v/v) 0.30

136c N-4-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from **136b** on a 1.48 mmol scale following the method described for **1f**. The product was isolated in 75% yield and used without further purification.

136d Methyl (3R)-4-{N-2-chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **136c** and **1c** on a 0.56 mmol scale following the method described for **1d**. The product was isolated in 70% yield after flash chromatography on silica gel (eluant EtOAc:hexane 45:55 v/v).

R_f (EtOAc:hexane 50:50 v/v) 0.26

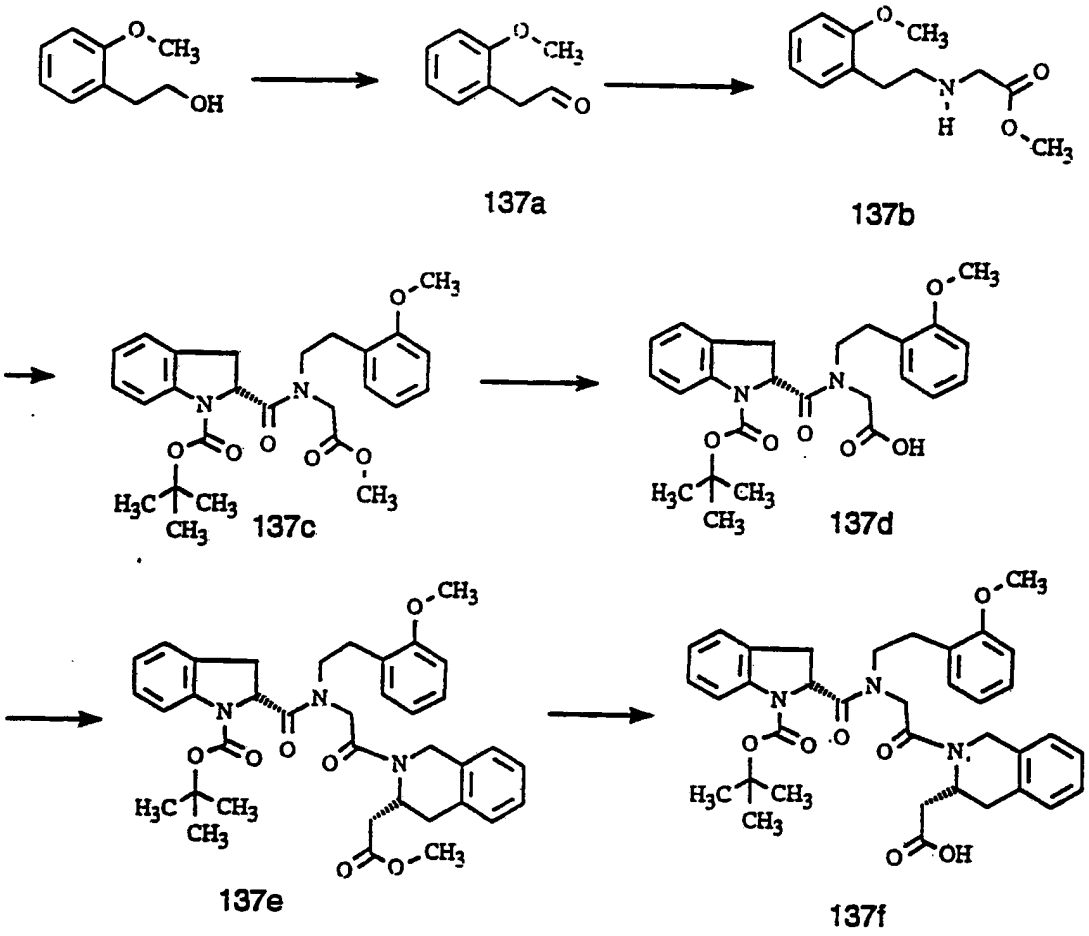
136e (3R)-2-{N-4-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **136d** on a 0.39 mmol scale following the method described for **1f**. The product was isolated in 60% yield (149 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:hexane:AcOH 65:35:2 v/v/v).

HPLC System A t_R=16.3' >95%

Mass spec (FAB) m/e=628 $[M+H]^+$

EXAMPLE 137



137a 137b 137c 137d 137e 137f

137a 2-Methoxyphenylacetaldehyde.

This was prepared from 2-methoxyphenethyl alcohol on a 13.1 mmol scale following the method described for **99a.** The product was isolated in 51% yield after flash chromatography on silica gel (eluant EtOAc:hexane 4:96 then 5:95 v/v).

R_f (EtOAc:hexane 5:95 v/v) 0.17

^1H NMR δ 3.57 (2H,d,J=2Hz); 3.75 (3H,s); 6.8-7.3 (4H,m); 9.61 (1H,t,J=2Hz)

137b Methyl N-2-methoxyphenethyl-glycinate.

This was prepared from **137a** on a 6.8 mmol scale following the method described for **42a.** The product was isolated in 28% yield after flash chromatography on silica gel (eluant EtOAc:hexane 80:20 v/v).

R_f (EtOAc:hexane 80:20 v/v) 0.16

137c Methyl N-2-methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.

This was prepared from **137b** and **48a** on a 1.9 mmol scale following the method described for **1d**. The product was isolated in 98% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R_f (EtOAc:hexane 50:50 v/v) 0.33

137d N-2-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from **137c** on a 1.90 mmol scale following the method described for **1f**. The product was isolated in 85% yield and used without further purification.

137e Methyl (3R)-2-{N-2-methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **137d** and **1c** on a 0.81 mmol scale following the method described for **1d**. The product was isolated in 92% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R_f (EtOAc:hexane 50:50 v/v) 0.28

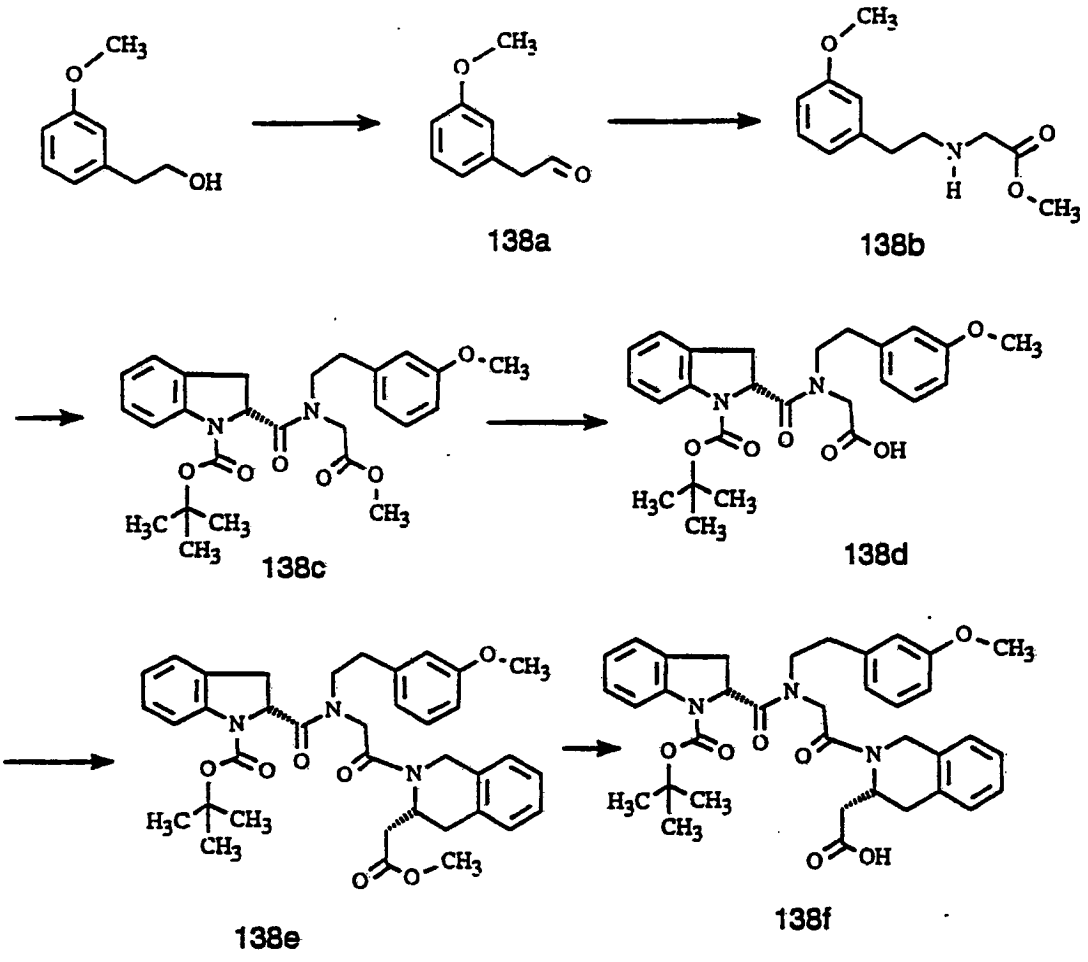
137f (3R)-2-{N-2-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **137e** on a 0.75 mmol scale following the method described for **1f**. The product was isolated in 52% yield (247 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 55:45:2 v/v).

HPLC System A t_R=21.1' >95%

Mass spec (FAB) m/e=628 $[M+H]^+$

EXAMPLE 138



138a 3-Methoxyphenylacetaldehyde.

This was prepared from 3-methoxyphenethyl alcohol on a 13.1 mmol scale following the method described for 99a. The product was isolated in 19% yield after flash chromatography on silica gel (eluant EtOAc:hexane 10:90 v/v).

R_f (EtOAc:hexane 10:90 v/v) 0.20

^1H NMR δ 3.58 (2H,d,J=2.5Hz); 3.73 (3H,s); 6.6-7.2 (4H,m); 9.67 (1H,t,J=2.5Hz)

138b Methyl N-3-methoxyphenethyl-glycinate.

This was prepared from 138a on a 2.6 mmol scale following the method described for 42a. The product was isolated in 42% yield after flash chromatography on silica gel (eluant EtOAc:hexane 90:10 v/v).

R_f (EtOAc:hexane 90:10 v/v) 0.16

138c Methyl N-3-methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.

This was prepared from **138b** and **48a** on a 1.1 mmol scale following the method described for **1d**. The product was isolated in 86% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).
R_f (EtOAc:hexane 40:60 v/v) 0.30

138d N-3-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from **138c** on a 0.93 mmol scale following the method described for **1f**. The product was used without further purification assuming a 100% yield.

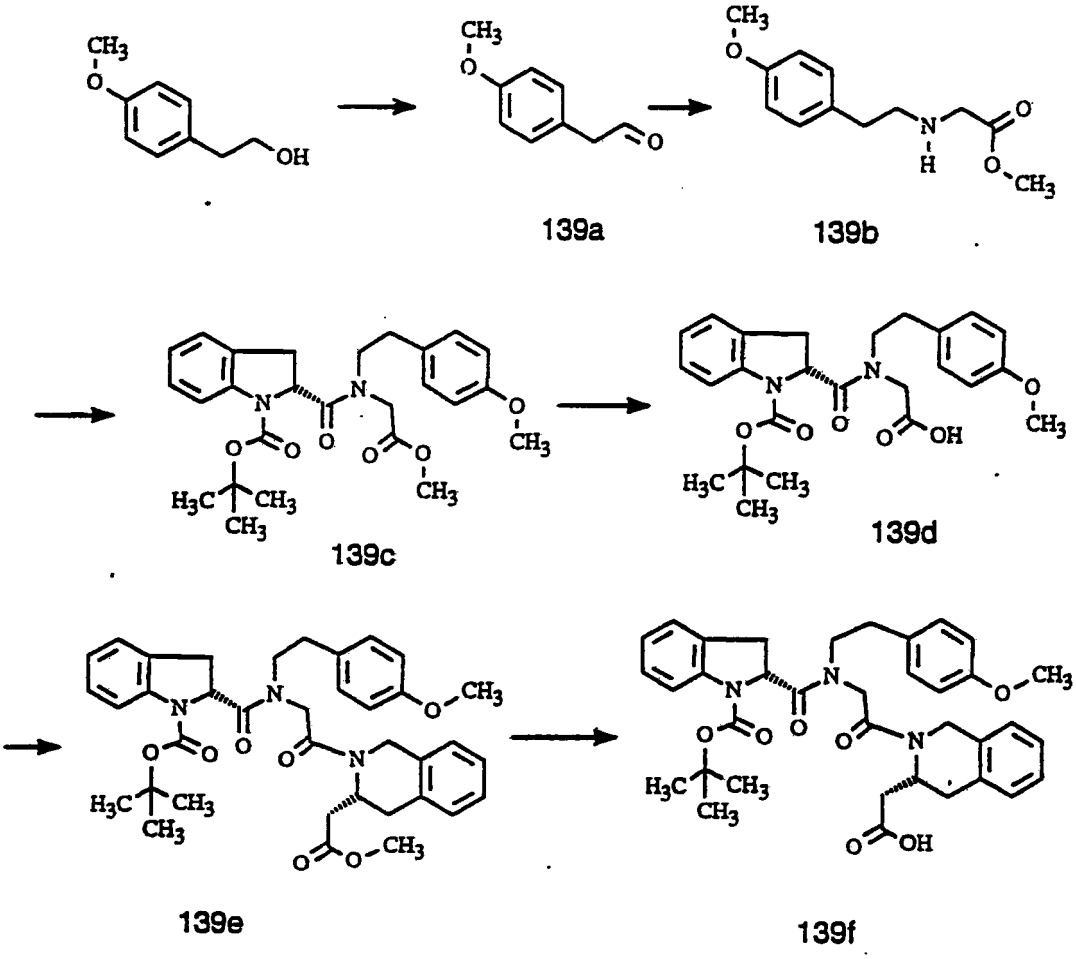
138e Methyl (3R)-2-{N-3-methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **138d** and **1c** on a 0.47 mmol scale following the method described for **1d**. The product was isolated in 91% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).
R_f (EtOAc:hexane 50:50 v/v) 0.23

138f (3R)-2-{N-3-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **138e** on a 0.43 mmol scale following the method described for **1f**. The product was isolated in 11% yield (31 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 55:45:2 v/v/v).
HPLC System A t_R=19.6' >80%
Mass spec (FAB) m/e=628 $[M+H]^+$

EXAMPLE 139



139a 4-Methoxyphenylacetaldehyde.

This was prepared from 4-methoxyphenethyl alcohol on a 13.1 mmol scale following the method described for **99a.** The product was isolated in 17% yield after flash chromatography on silica gel (eluant EtOAc:hexane 10:90 v/v).

R_f (EtOAc:hexane 10:90 v/v) 0.20

^1H NMR δ 3.75 (2H,d,J=2.3Hz); 3.75 (3H,s); 7.03 (2H,d,J=9Hz); 7.25 (2H,d,J=9Hz); 9.84 (1H,t,J=2.3Hz)

139b Methyl N-4-methoxyphenethyl-glycinate.

This was prepared from **139a** on a 2.3 mmol scale following the method described for **42a.** The product was isolated in 38% yield after flash chromatography on silica gel (eluant EtOAc:hexane 90:10 v/v).

R_f (EtOAc:hexane 90:10 v/v) 0.17

139c Methyl N-4-methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.

This was prepared from **139b** and **48a** on a 0.87 mmol scale following the method described for **1d**. The product was isolated in 82% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R_f (EtOAc:hexane 50:50 v/v) 0.30

139d N-4-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from **139c** on a 0.72 mmol scale following the method described for **1f**. The product was isolated in 80% yield and used without further purification.

139e Methyl (3R)-2-{N-4-methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **139d** and **1c** on a 0.29 mmol scale following the method described for **1d**. The product was isolated in 75% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R_f (EtOAc:hexane 50:50 v/v) 0.21

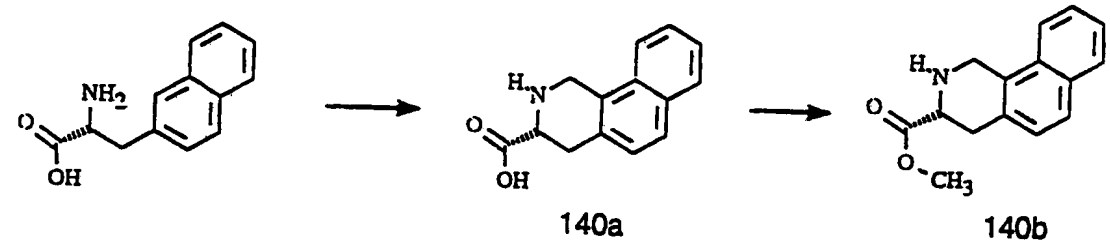
139f (3R)-2-{N-4-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **139e** on a 0.22 mmol scale following the method described for **1f**. The product was isolated in 47% yield (65 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 55:45:2 v/v/v).

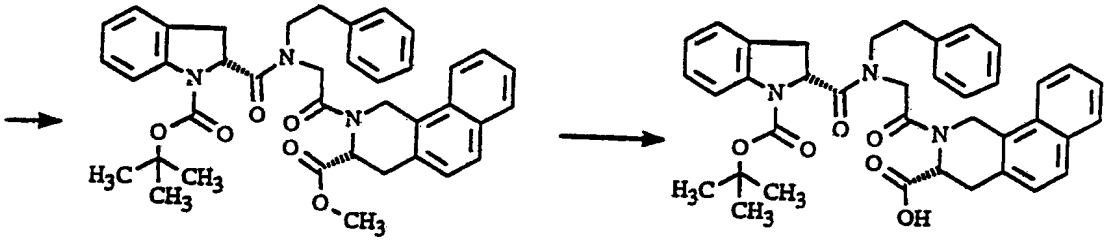
HPLC System A t_R=19.6' >80%

Mass spec (FAB) m/e=628 $[M+H]^+$

EXAMPLE 140



140a 140b



140c 140d

140a 1,2,3,4-Tetrahydro-benz[h]isoquinoline-3-carboxylic acid.

This was prepared from β-(2-naphthyl)alanine on a 23 mmol scale following the method described for **84a**. The product was isolated in 85% yield as a mixture of benz[g]- and benz[h]-fused isomers which was used without further purification.

140b Methyl 1,2,3,4-tetrahydro-benz[h]isoquinoline-3-carboxylate.

This was prepared from **140a** on a 9.9 mmol scale following the method described for **26a**. The product was isolated in 2% yield after flash chromatography on silica gel (eluant EtOAc). The benz[g]-fused isomer was also isolated (in 4% yield).

140c Methyl (3R)-2-{N-phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[h]isoquinoline-3-carboxylate.

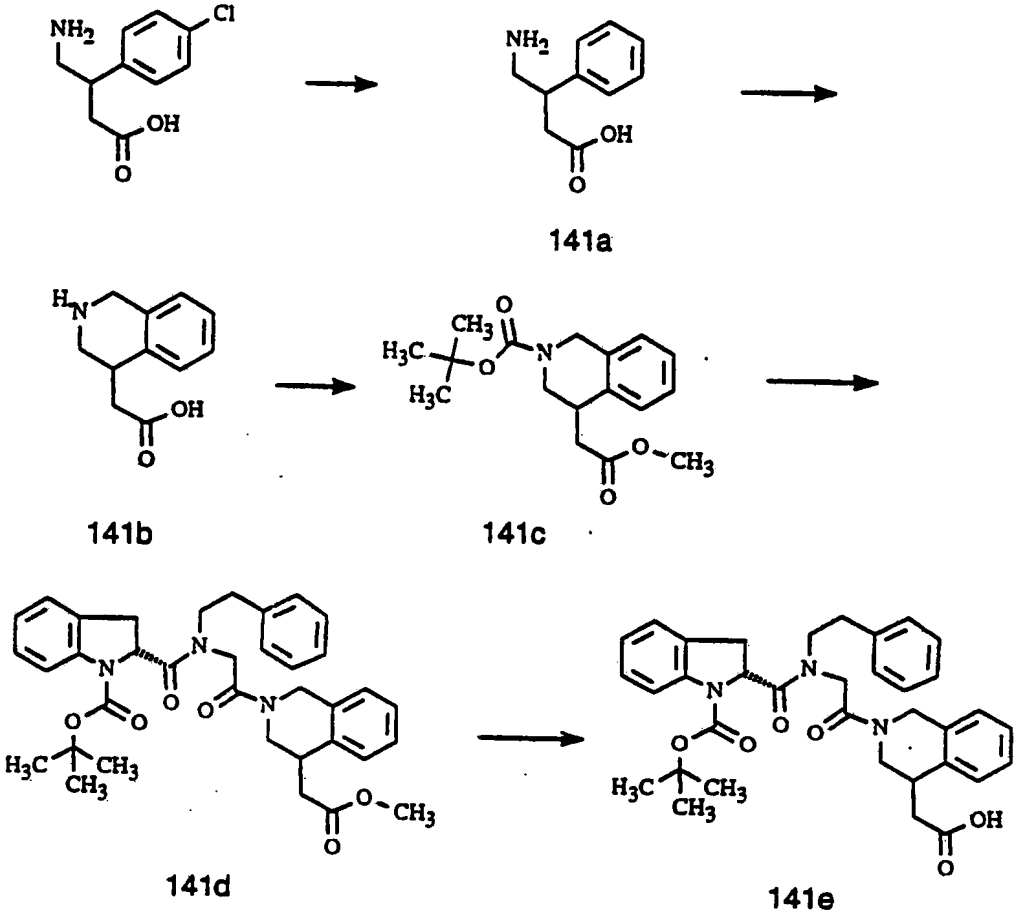
This was prepared from **90b** and **140b** on a 0.19 mmol scale following the method described for **1d**. The product was isolated in 33% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

140d (3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[h]isoquinoline-3-carboxylic acid.

This was prepared from 140c on a 0.06 mmol scale following the method described for **1f**. The product was isolated in 47% yield (18 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 70:30:2 v/v/v).

HPLC System A t_R=21.9' >80%
Mass spec (FAB) m/e=407

EXAMPLE 141



141a (3RS)-4-Amino-3-phenylbutanoic acid.

A suspension of (RS)-4-amino-3-(4-chlorophenyl)butanoic acid in H_2O (100 mL) and MeOH (70 mL) was hydrogenated over 5% Pd-on-carbon at room temperature for 5 hr. The mixture was filtered through Celite and the filtrate was concentrated *in vacuo* to give the title compound which was used without further purification assuming a yield of 100%.

141b (4RS)-1,2,3,4-Tetrahydroisoquinoline-4-acetic acid.

This was prepared from **141a** on a 4.7 mmol scale following the method described for **84a**. The product was used without further purification assuming a yield of 100%.

141c Methyl (4RS)-2-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-4-acetate.

This was prepared from **141b** on a 4.7 mmol scale in two steps. The acid was esterified following the method described for **26a**. The crude product was taken up in CH_2Cl_2 (70 mL) and treated with BOC_2O (1.31 g, 6 mmol) and *i*-Pr_2NEt (excess). The mixture was stirred at room temperature overnight, dilutede with EtOAc, washed with aq. $KHSO_4$ and brine, filtered (Whatman 1PS phase separator), and concentrated *in vacuo*. The product was isolated in 25% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).

141d Methyl (4RS)-2-{N-phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-4-acetate.

This was prepared from **90b** and **141c** on a 0.50 mmol scale following the method described for **79d**. The product was isolated in 39% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

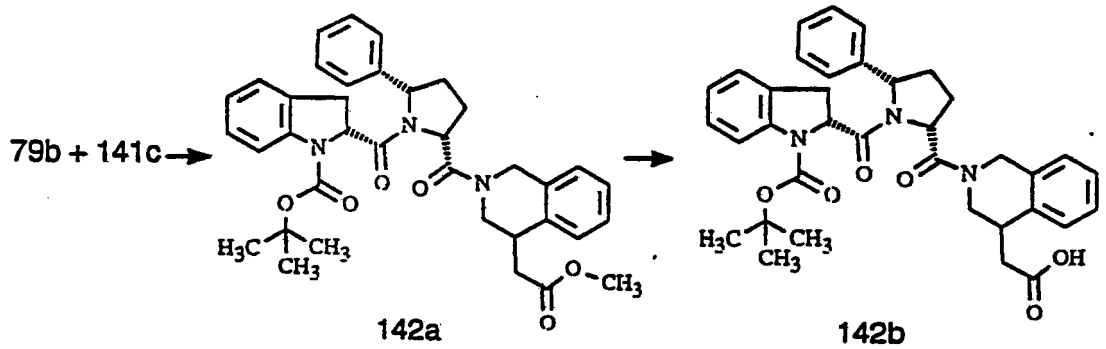
141e (4RS)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-4-acetic acid.

This was prepared from **141d** on a 0.19 mmol scale following the method described for **1f**. The product was isolated in 70% yield (79 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).

HPLC System A t_R=19.0' >90%

Mass spec (FAB) m/e=598 $[M+H]^+$

EXAMPLE 142



142a Methyl (4RS)-2-{(2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-4-acetate.

This was prepared from **79b** and **141c** on a 0.52 mmol scale following the method described for **79d**. The product was isolated in 48% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

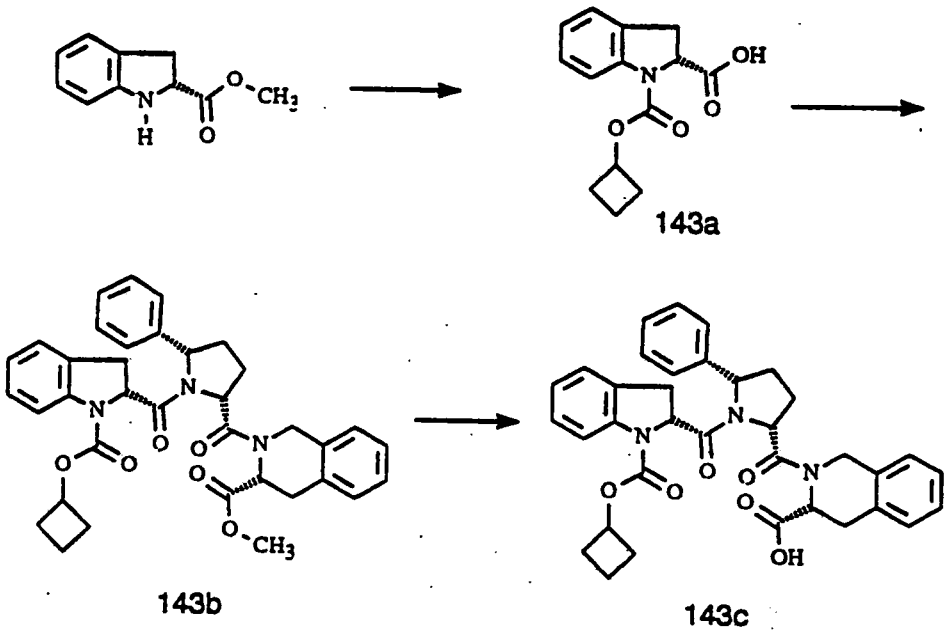
142b (4RS)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-4-acetic acid.

This was prepared from **142a** on a 0.16 mmol scale following the method described for **1f**. The product was isolated in 71% yield (69 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 50:50:2 v/v/v).

HPLC System A t_R=20.2' >95%

Mass spec (FAB) m/e=610 $[M+H]^+$

EXAMPLE 143



143a (2R)-1-Cyclobutyloxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from cyclobutanol on a 2.0 mmol scale following the method described for **72a**. The product was isolated in 16% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 35:65:2 v/v/v).

143b Methyl (3R)-2-{(2R,5S)-1-((2R)-1-cyclobutyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **68a** and **143a** on a 0.24 mmol scale following the method described for **79d**. The product was isolated in 82% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

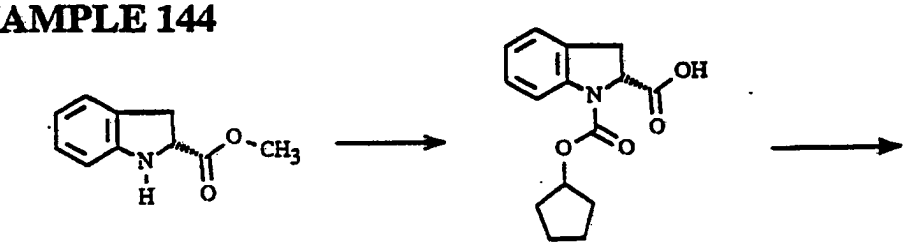
143c (3R)-2-{(2R,5S)-1-((2R)-1-Cyclobutyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **143b** on a 0.20 mmol scale following the method described for **1f**. The product was isolated in 72% yield (85 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 65:35:2 v/v/v).

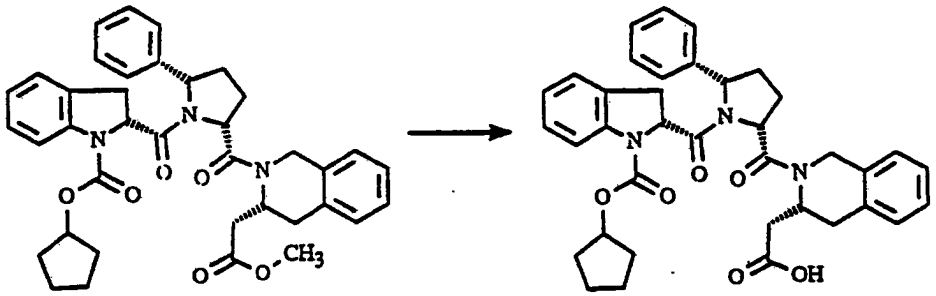
HPLC System B t_R=14.2' >95%

Mass spec (FAB) m/e=594 $[M+H]^+$

EXAMPLE 144



144a



144b 144c

144a (2R)-1-Cyclopentyloxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from cyclopentanol on a 2.0 mmol scale following the method described for **72a**. The product was isolated in 75% yield and used without purification.

144b Methyl (3R)-2-{(2R.5S)-1-((2R)-1-cyclopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1.2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **78a** and **144a** on a 0.30 mmol scale following the method described for **79d**. The product was isolated in 73% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

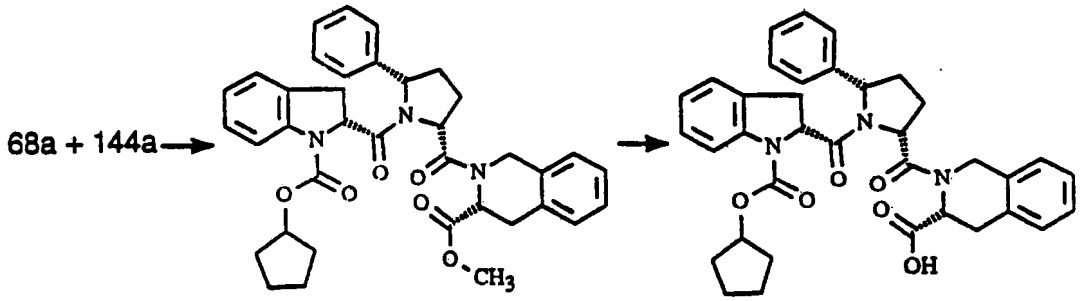
144c (3R)-2-{(2R.5S)-1-((2R)-1-Cyclopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1.2.3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **144b** on a 0.22 mmol scale following the method described for **1f**. The product was isolated in 79% yield (108 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 65:35:2 v/v/v).

HPLC System B t_R=16.3' >98%

Mass spec (FAB) m/e=622 $[M+H]^+$

EXAMPLE 145



145a 145b

145a Methyl (3R)-2-{(2R.5S)-1-((2R)-1-cyclopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **68a** and **144a** on a 0.24 mmol scale following the method described for **79d**. The product was isolated in 81% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

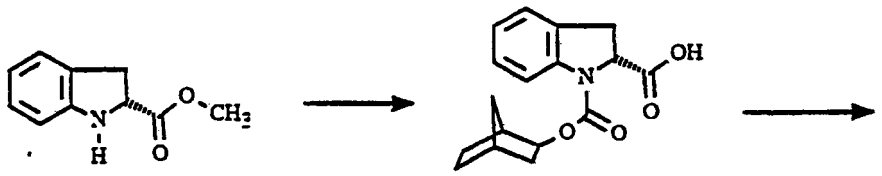
145b (3R)-2-{(2R,5S)-1-((2R)-1-Cyclopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **145a** on a 0.19 mmol scale following the method described for **1f**. The product was isolated in 69% yield (80 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 65:35:2 v/v/v).

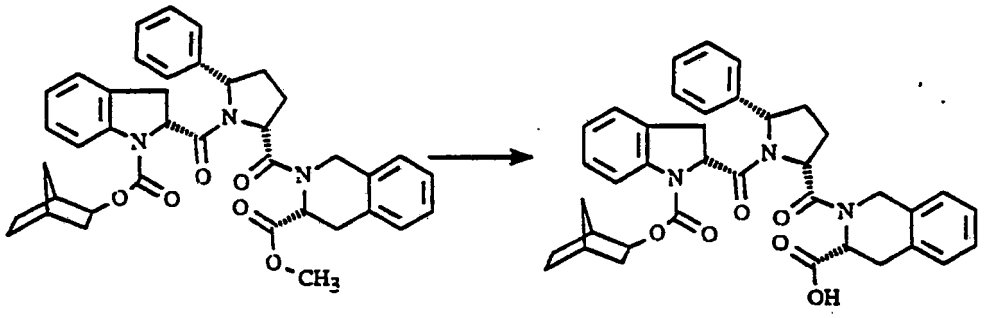
HPLC System B t_R=15.2' >98%

Mass spec (FAB) m/e=608 $[M+H]^+$

EXAMPLE 146



146a



146b 146c

146a (2R)-1-(2-*exo*-Norbornyl)oxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from 2-*exo*-norbornyl alcohol on a 1.0 mmol scale following the method described for **72a**. The product was isolated in 93% yield and used without purification.

146b Methyl (3R)-2-{(2R,5S)-1-((2R)-1-(2-*exo*-norbornyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **68a** and **146a** on a 0.24 mmol scale following the method described for **79d**. The product was isolated in 74% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

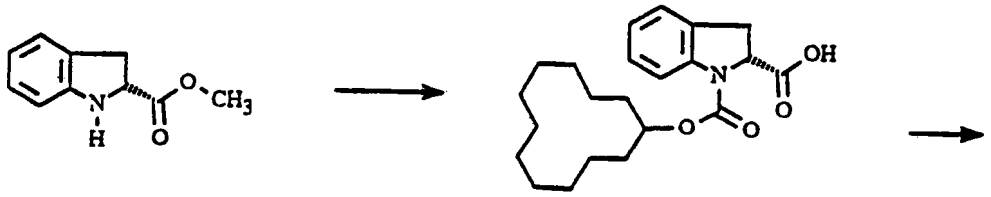
146c (3R)-2-{(2R,5S)-1-((2R)-1-(2-*exo*-Norbornyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **146b** on a 0.18 mmol scale following the method described for **1f**. The product was isolated in 65% yield (74 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 60:40:2 v/v/v).

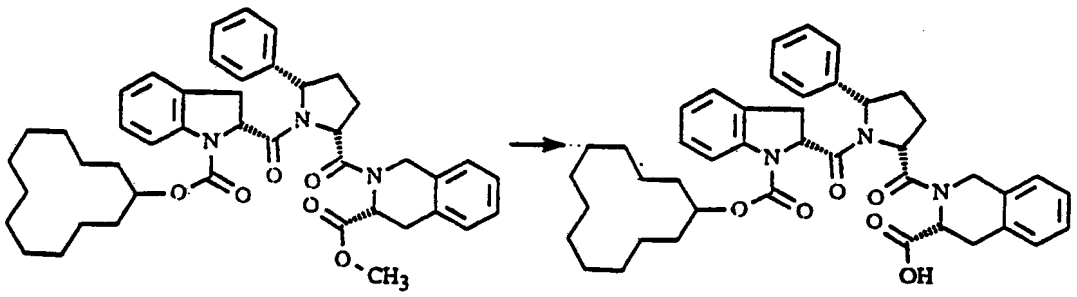
HPLC System B t_R=17.2' >98%

Mass spec (FAB) m/e=634 $[M+H]^+$

EXAMPLE 147



147a



147b 147c

147a (2R)-1-Cyclododecyloxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from cyclododecanol on a 1.0 mmol scale following the method described for **72a**. The product was isolated in 64% yield and used without purification.

147b Methyl (3R)-2-{(2R,5S)-1-((2R)-1-cyclododecyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **68a** and **147a** on a 0.24 mmol scale following the method described for **79d**. The product was isolated in 55% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

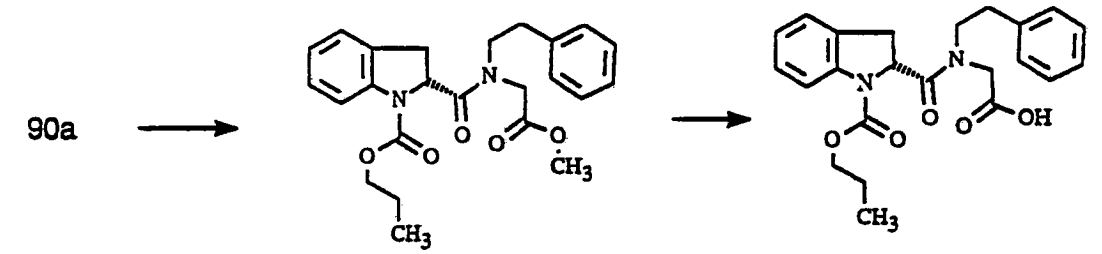
147c (3R)-2-{(2R.5S)-1-((2R)-1-Cyclododecyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1.2.3.4-tetrahydroisoquinoline-3-carboxylic acid.

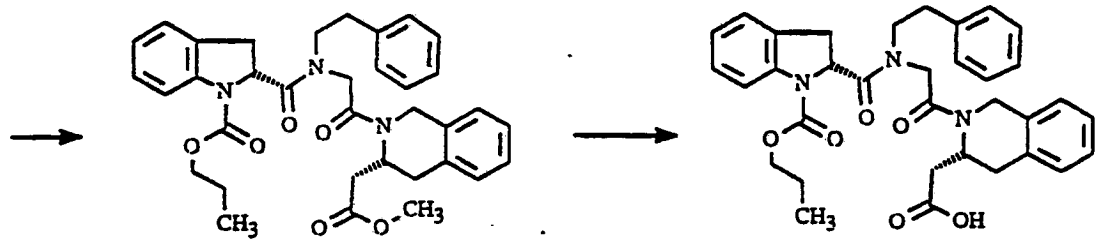
This was prepared from **147b** on a 0.13 mmol scale following the method described for **1f**. The product was isolated in 58% yield (53 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 55:45:2 v/v/v).

HPLC System B t_R=25.0' >98%

Mass spec (FAB) m/e=706 $[M+H]^+$

EXAMPLE 148





148a Methyl N-phenethyl-N-((2R)-1-*n*-propyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-glycinate.

This was prepared from **90a** and propyl chloroformate on a 0.48 mmol scale following the method described for **81a**. The product was isolated in 88% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 35:65 v/v).

148b N-Phenethyl-N-((2R)-1-*n*-propyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from **148a** on a 0.42 mmol scale following the method described for **1f**. The product was isolated in 45% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 65:35:2 v/v/v).

148c Methyl (3R)-2-{N-phenethyl-N-((2R)-1-*n*-propyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **1c** and **148b** on a 0.08 mmol scale following the method described for **1d**. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 55:45 v/v).

R_f (EtOAc:hexane 60:40 v/v) 0.35

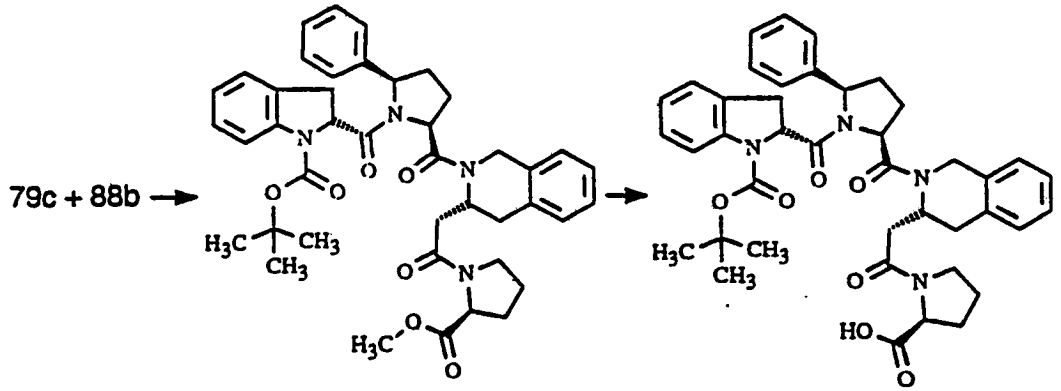
148d (3R)-2-{N-Phenethyl-N-((2R)-1-*n*-propyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **148c** on a 0.08 mmol scale following the method described for **1f**. The product was isolated in 54% yield (25 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 70:30:2 v/v/v).

HPLC System A t_R=17.9' >98%

Mass spec (FAB) m/e=584 $[M+H]^+$

EXAMPLE 149



149a 149b

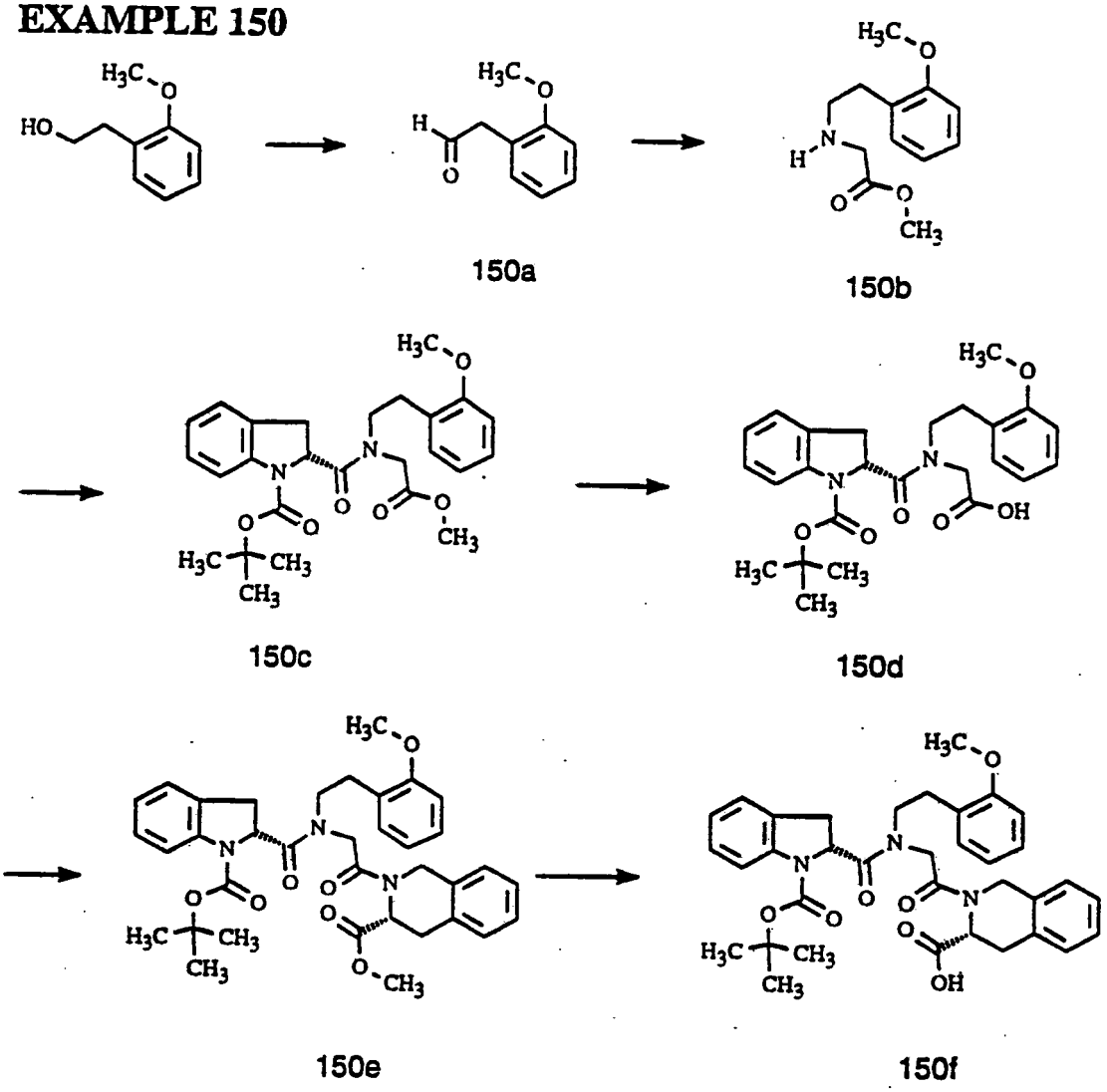
149a Methyl N-{(3R)-2-{(2S,5R)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetyl}-prolinate.

This was prepared from **79c** and **88b** on a 0.14 mmol scale following the method described for **79d**. The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 80:20 v/v).
R_f (EtOAc:hexane 80:20 v/v) 0.13

149b N-{(3R)-2-{(2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetyl}-proline.

This was prepared from **149a** on a 0.14 mmol scale following the method described for **1f**. The product was isolated in 46% yield (46 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).
HPLC System A t_R=17.6' >95%
AAA Peptide content=91%
Mass spec (FAB) m/e=707 $[M+H]^+$

EXAMPLE 150



150a (2-Methoxyphenyl)acetaldehyde.

This was prepared from 2-(2-methoxyphenyl)ethanol on a 13.1 mmol scale following the method described for **99ad.** The product was isolated in 52% yield after flash chromatography on silica gel (eluant EtOAc:hexane 5:95 v/v).

R_f (EtOAc:hexane 5:95 v/v) 0.17

150b Methyl N-2-(2-methoxyphenyl)ethyl-glycinate.

This was prepared from **150a** on a 6.8 mmol scale following the method described for **42a.** The product was isolated in 28% yield after flash chromatography on silica gel (eluant EtOAc:hexane 80:20 v/v).

R_f (EtOAc:hexane 80:20 v/v) 0.16

150c Methyl N-2-(2-methoxyphenyl)ethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.

This was prepared from **48a** and **150b** on a 1.93 mmol scale following the method described for **1d**. The product was isolated in 98% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R_f (EtOAc:hexane 50:50 v/v) 0.33

150d N-2-(2-Methoxyphenyl)ethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from **150c** on a 1.90 mmol scale following the method described for **1f**. The product was isolated in 85% yield and used without purification.

150e Methyl (3R)-2-{N-2-(2-methoxyphenyl)ethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **26a** and **150d** on a 0.81 mmol scale following the method described for **1d**. The product was isolated in 94% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R_f (EtOAc:hexane 40:60 v/v) 0.29

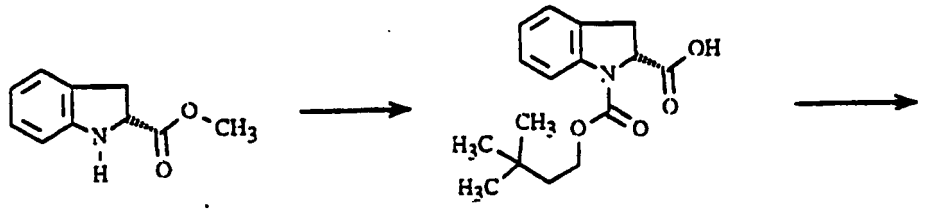
150f (3R)-2-{N-2-(2-Methoxyphenyl)ethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **150e** on a 0.76 mmol scale following the method described for **1f**. The product was isolated in 57% yield (267 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 55:45:2 v/v/v).

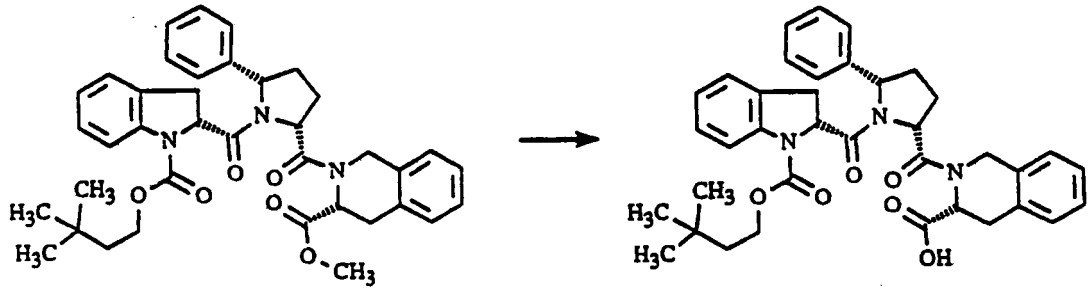
HPLC System A t_R=20.5' >95%

Mass spec (FAB) m/e=614 $[M+H]^+$

EXAMPLE 151



151a



151b 151c

151a (2R)-1-(3,3-Dimethylbutyl)oxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from 3.3-dimethylbutanol on a 2.34 mmol scale following the method described for **72a.** The product was isolated in 37% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 35:65:2 v/v/v).

151b Methyl (3R)-2-{(2R.5S)-1-((2R)-1-(3,3-dimethylbutyl)oxycarbonyl-2.3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **68a** and **151a** on a 0.28 mmol scale following the method described for **79d.** The product was isolated in 75% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

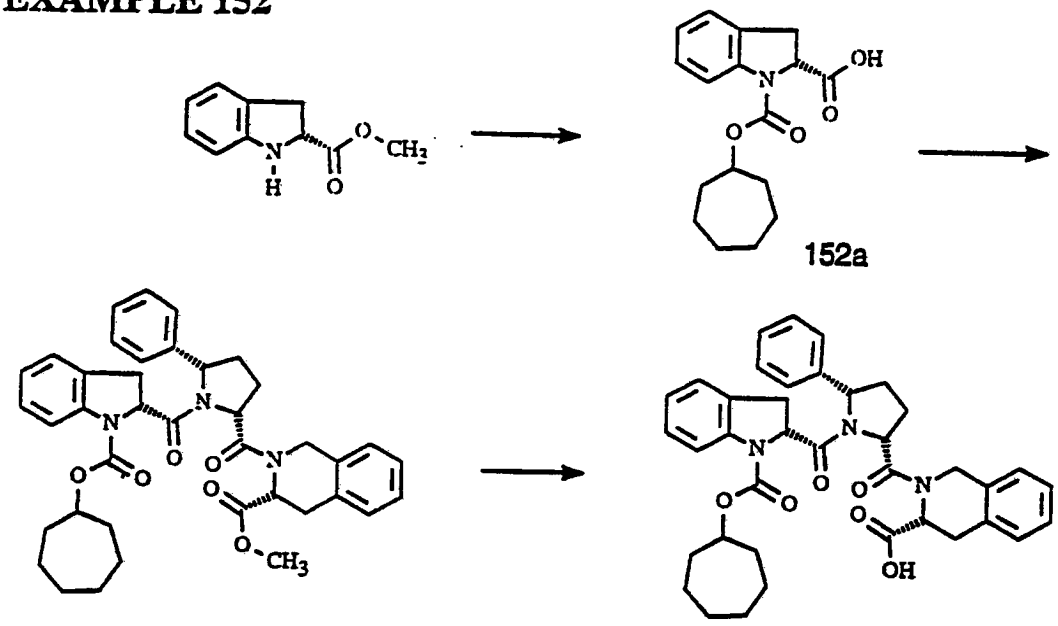
R_f (EtOAc:hexane 35:65 v/v) 0.21

151c (3R)-2-{(2R.5S)-1-((2R)-1-(3,3-Dimethylbutyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **151b** on a 0.21 mmol scale following the method described for **1f.** The product was isolated in 66% yield (87 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 45:55:2 v/v/v).

HPLC System B t_R=17.8' >95%
Mass spec (FAB) m/e=624 $[M+H]^+$

EXAMPLE 152



152a

152b

152c

152a 1-((2R)-1-Cycloheptyloxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from cycloheptanol on a 2.35 mmol scale following the method described for **72a.** The product was isolated in 39% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 35:65:2 v/v/v).

152b Methyl (3R)-2-{(2R,5S)-1-((2R)-1-cycloheptyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **68a** and **152a** on a 0.28 mmol scale following the method described for **79d.** The product was isolated in 86% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).
R_f (EtOAc:hexane 35:65 v/v) 0.22

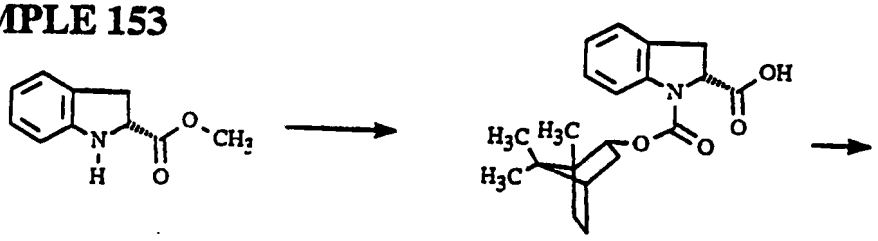
152c (3R)-2-{(2R.5S)-1-((2R)-1-Cycloheptyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1.2.3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **152b** on a 0.24 mmol scale following the method described for **1f**. The product was isolated in 51% yield (78 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 45:55:2 v/v/v).

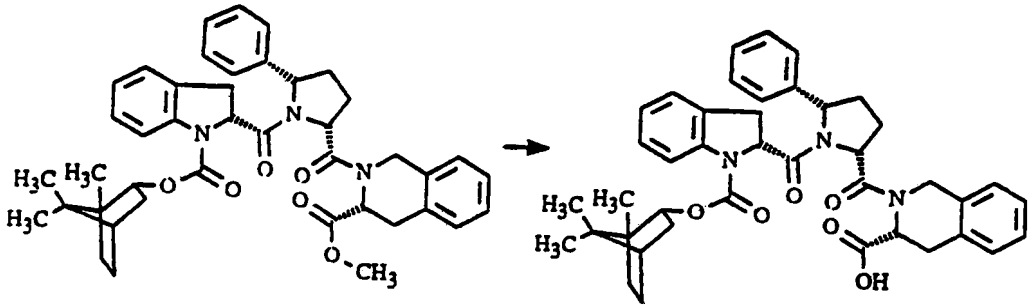
HPLC System B t_R=18.2' >98%

Mass spec (FAB) m/e=636 $[M+H]^+$

EXAMPLE 153



153a



153b 153c

153a (2R)-1-((1S)-*endo*-Bornyl)oxycarbonyl-2.3-dihydroindole-2-carboxylic acid.

This was prepared from (1S)-*endo*-borneol on a 2.34 mmol scale following the method described for **72a**. The product was isolated in 59% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 35:65:2 v/v/v).

153b Methyl (3R)-2-{(2R.5S)-1-((2R)-1-((1S)-*endo*-bornyl)oxycarbonyl-2.3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **68a** and **153a** on a 0.28 mmol scale following the method described for **79d**. The product was isolated in 66% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

R_f (EtOAc:hexane 35:65 v/v) 0.28

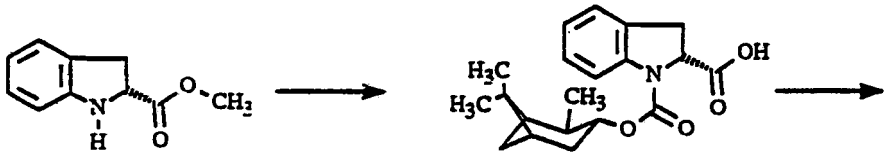
153c (3R)-2-{(2R,5S)-1-((2R)-1-((1S)-*endo*-Bornyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **153b** on a 0.19 mmol scale following the method described for **1f**. The product was isolated in 47% yield (62 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 45:55:2 v/v/v).

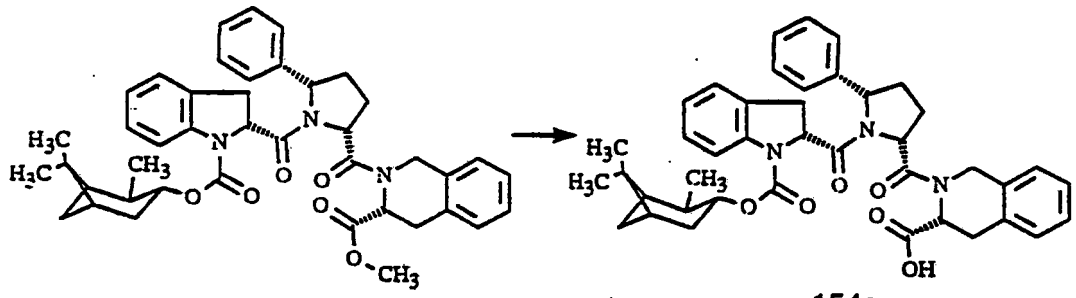
HPLC System B t_R=20.6' >95%

Mass spec (FAB) m/e=676 $[M+H]^+$

EXAMPLE 154



154a



154b 154c

154a (2R)-1-((1R,2R,3R,5S)-Isopinocampheyl)oxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from (1R,2R,3R,5S)-isopinocampheol on a 2.34 mmol scale following the method described for **72a.** The product was isolated in 57% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 35:65:2 v/v/v).

154b Methyl (3R)-2-{(2R,5S)-1-((2R)-1-((1R,2R,3R,5S)-isopinocampheyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **68a** and **154a** on a 0.28 mmol scale following the method described for **79d**. The product was isolated in 70% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

R_f (EtOAc:hexane 35:65 v/v) 0.28

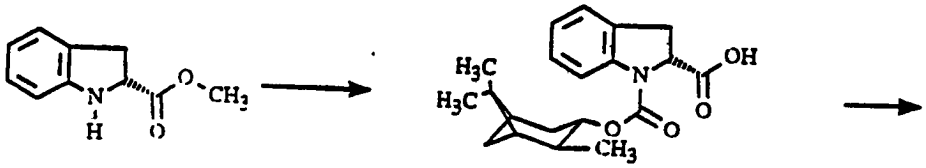
154c (3R)-2-{(2R,5S)-1-((2R)-1-((1R,2R,3R,5S)-Isopinocampheyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **154b** on a 0.20 mmol scale following the method described for **1f**. The product was isolated in 53% yield (73 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 45:55:2 v/v/v).

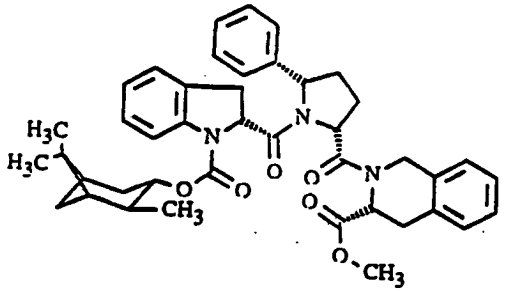
HPLC System B t_R=21.0' >95%

Mass spec (FAB) m/e=676 $[M+H]^+$

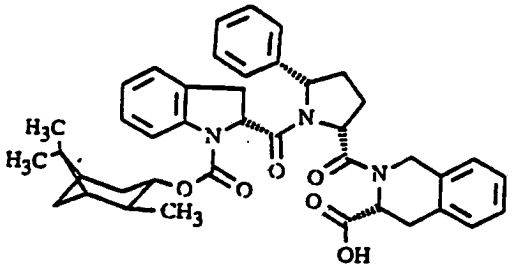
EXAMPLE 155



155a



155b



155c

155a (2R)-1-((1S.2S.3S.5R)-Isopinocampheyl)oxycarbonyl-2.3-dihydroindole-2-carboxylic acid.

This was prepared from (1S.2S.3S.5R)-isopinocampheol on a 2.34 mmol scale following the method described for **72a**. The product was isolated in 69% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 35:65:2 v/v/v).

155b Methyl (3R)-2-{(2R.5S)-1-((2R)-1-((1S.2S.3S,5R)-isopinocampheyl)oxycarbonyl-2.3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **68a** and **155a** on a 0.28 mmol scale following the method described for **79d**. The product was isolated in 75% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

R_f (EtOAc:hexane 35:65 v/v) 0.27

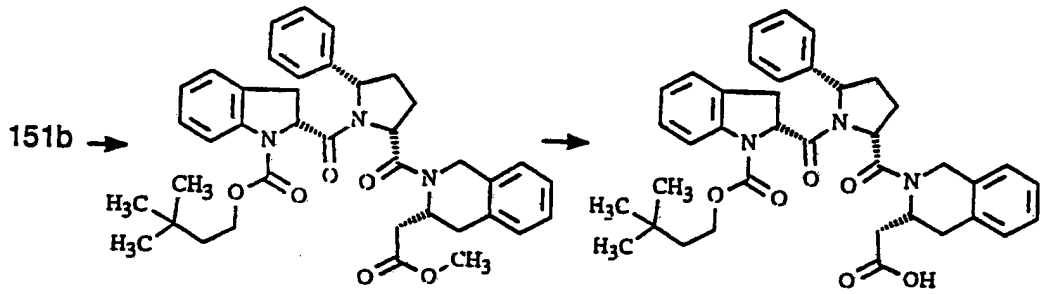
155c (3R)-2-{(2R,5S)-1-((2R)-1-((1S.2S.3S.5R)-Isopinocampheyl)oxycarbonyl-2.3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **155b** on a 0.21 mmol scale following the method described for **1f**. The product was isolated in 39% yield (56 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 45:55:2 v/v/v).

HPLC System B t_R=21.3' >98%

Mass spec (FAB) m/e=676 $[M+H]^+$

EXAMPLE 156



156a Methyl (3R)-2-{(2R,5S)-1-((2R)-1-(3,3-dimethylbutyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **78a** and **151a** on a 0.30 mmol scale following the method described for **79d**. The product was isolated in 77% yield after flash chromatography on silica gel (eluant EtOAc:hexane 35:65 v/v).

R_f (EtOAc:hexane 50:50 v/v) 0.49

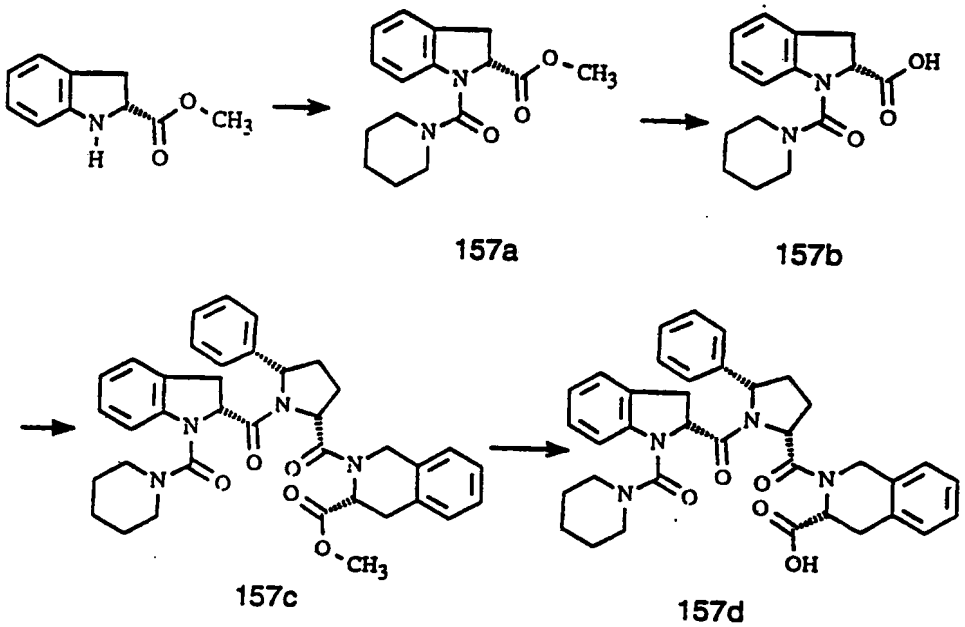
156b (3R)-2-{(2R,5S)-1-((2R)-1-(3,3-Dimethylbutyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **156a** on a 0.23 mmol scale following the method described for **1f**. The product was isolated in 44% yield (65 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 45:55:2 v/v/v).

HPLC System B t_R=19.0' >98%

Mass spec (FAB) m/e=660 $[M+Na]^+$

EXAMPLE 157



157a Methyl (2R)-1-(1-piperidino)carbonyl-2.3-dihydroindole-2-carboxylate.

This was prepared from piperidine on a 1.64 mmol scale following the method described for **72a** but without the final hydrolysis. The product was isolated in 44% yield after flash chromatography on silica gel (eluant EtOAc:hexane 30:70 v/v).

R_f (EtOAc:hexane 30:70 v/v) 0.14

157b (2R)-1-(1-Piperidino)carbonyl-2.3-dihydroindole-2-carboxylic acid.

This was prepared from **157a** on a 0.71 mmol scale following the method described for **1f**. The product was isolated in 72% yield and used without purification.

157c Methyl (3R)-2-{(2R.5S)-1-((2R)-1-(1-piperidino)carbonyl-2.3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1.2.3.4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **68a** and **157b** on a 0.51 mmol scale following the method described for **79d**. The product was isolated in 54% yield after flash chromatography on silica gel (eluant EtOAc:hexane 70:30 v/v).

R_f (EtOAc:hexane 70:30 v/v) 0.16

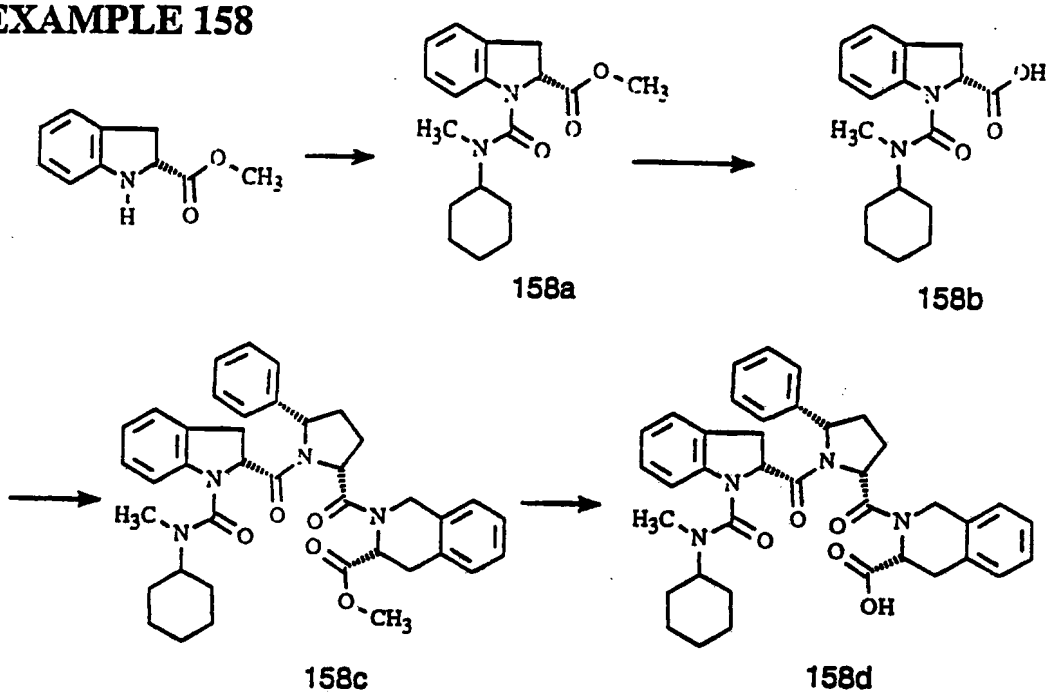
157d (3R)-2-{(2R.5S)-1-((2R)-1-(1-Piperidino)carbonyl-2.3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1.2,3.4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **157c** on a 0.28 mmol scale following the method described for **1f**. The product was isolated in 18% yield (30 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

HPLC System B t_R=14.9' >98%

Mass spec (FAB) m/e=607 $[M+H]^+$

EXAMPLE 158



158a 158b 158c 158d

158a Methyl (2R)-1-(N-cyclohexyl-N-methylcarbamoyl)-2,3-dihydroindole-2-carboxylate.

This was prepared from N-methyl-cyclohexylamine on a 1.64 mmol scale following the method described for **157a**. The product was isolated in 25% yield after flash chromatography on silica gel (eluant EtOAc:hexane 15:85 v/v).

R_f (EtOAc:hexane 30:70 v/v) 0.20

158b (2R)-1-(N-Cyclohexyl-N-methylcarbamoyl)-2.3-dihydroindole-2-carboxylic acid.

This was prepared from **158a** on a 0.60 mmol scale following the method described for **1f**. The product was isolated in 67% yield and used without purification.

158c Methyl (3R)-2-{(2R.5S)-1-((2R)-1-(N-cyclohexyl-N-methylcarbamoyl)-2.3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **68a** and **158b** on a 0.40 mmol scale following the method described for **79d**. The product was isolated in 72% yield after flash chromatography on silica gel (eluant EtOAc:hexane 55:45 v/v).

R_f (EtOAc:hexane 70:30 v/v) 0.25

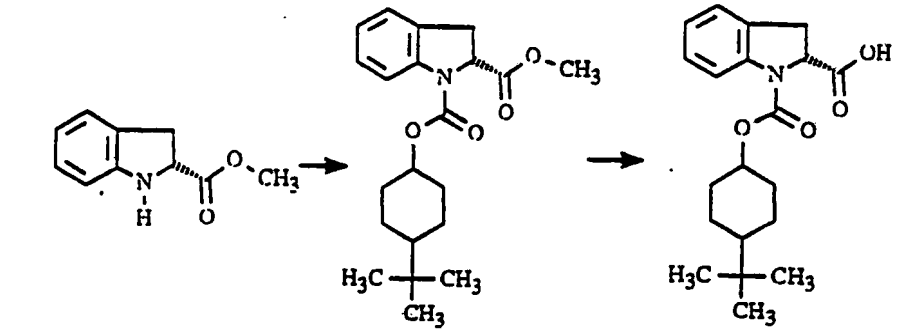
158d (3R)-2-{(2R.5S)-1-((2R)-1-(N-Cyclohexyl-N-methylcarbamoyl)-2.3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1.2.3.4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **158c** on a 0.29 mmol scale following the method described for 1f. The product was isolated in 33% yield (60 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 85:15:2 v/v/v).

HPLC System B t_R=17.6' >99%

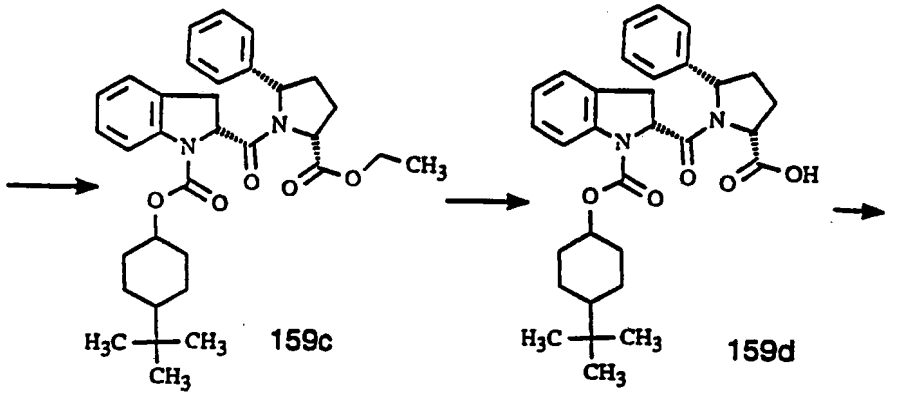
Mass spec (FAB) m/e=635 $[M+H]^+$

EXAMPLE 159



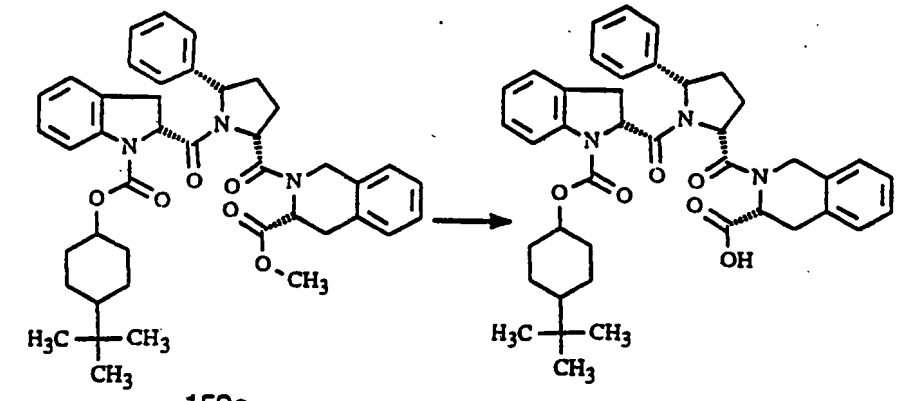
159a

159b



159c

159d



159e

159f

159a Methyl (2R)-1-(4-*tert*-butylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carboxylate.

This was prepared from 4-*tert*-butylcyclohexanol on a 1.64 mmol scale following the method described for 157a. The product was isolated in 50% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 20:80:2 v/v/v).

159b (2R)-1-(4-*tert*-Butylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from **159a** on a 0.82 mmol scale following the method described for **1f**. The product was used without purification, assuming a yield of 100%.

159c Ethyl (2R,5S)-1-((2R)-1-(4-*tert*-butylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carboxylate.

This was prepared from **30a** and **159b** on a 0.82 mmol scale following the method described for **1d**. The product was isolated in 34% yield after flash chromatography on silica gel (eluant EtOAc:hexane 20:80 v/v).

R_f (EtOAc:hexane 40:60 v/v) 0.46

159d (2R,5S)-1-((2R)-1-(4-*tert*-Butylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carboxylic acid.

This was prepared from **159c** on a 0.28 mmol scale following the method described for **1f**. The product was used without purification, assuming a yield of 100%.

159e Methyl (3R)-2-{(2R,5S)-1-((2R)-1-(4-*tert*-butylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **26a** and **159d** on a 0.28 mmol scale following the method described for **1d**. The product was isolated in 93% yield after flash chromatography on silica gel (eluant EtOAc:hexane 30:70 v/v).

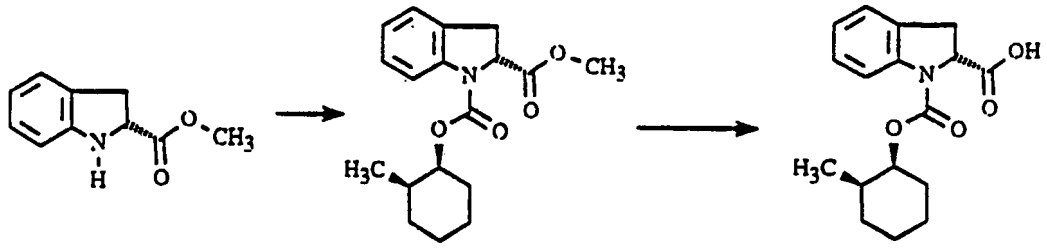
159f (3R)-2-{(2R,5S)-1-((2R)-1-(4-*tert*-Butylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **159e** on a 0.26 mmol scale following the method described for **1f**. The product was isolated in 35% yield (62 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 65:35:2 v/v/v).

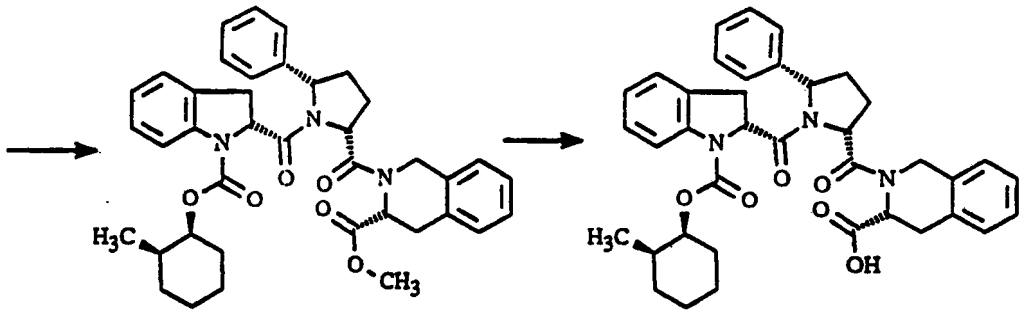
HPLC System B t_R=23.0' >95%

Mass spec (FAB) m/e=678 $[M+H]^+$

EXAMPLE 160



160a 160b



160c 160d

160a Methyl (2R)-1-(2-*cis*-methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carboxylate.

This was prepared from (±)-2-*cis*-methylcyclohexanol on a 3.28 mmol scale following the method described for **157a**. The product was isolated in 51% yield after flash chromatography on silica gel (eluant EtOAc:hexane 20:80 v/v).
R_f (EtOAc:hexane 30:70 v/v) 0.41

160b (2R)-1-(2-*cis*-Methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from **160a** on a 1.66 mmol scale following the method described for **1f**. The product was isolated in 23% yield and used without purification.

160c Methyl (3R)-2-{(2R,5S)-1-((2R)-1-(2-*cis*-methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **68a** and **160b** on a 0.38 mmol scale following the method described for **79d**. The product was isolated in 25% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 25:75:1 v/v/v).

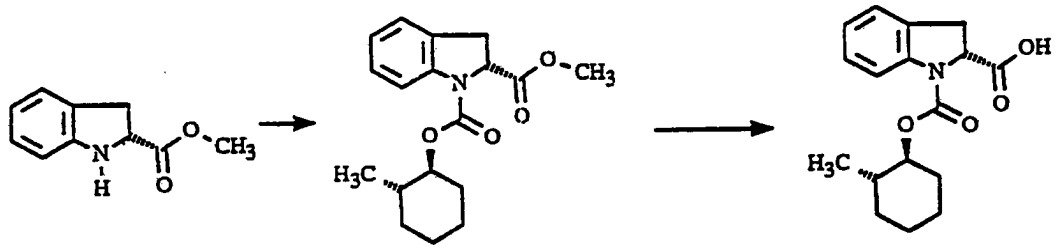
160d (3R)-2-{(2R,5S)-1-((2R)-1-(2-*cis*-Methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from 160c on a 0.09 mmol scale following the method described for 1f. The product was isolated in 48% yield (29 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 70:30:2 v/v/v).

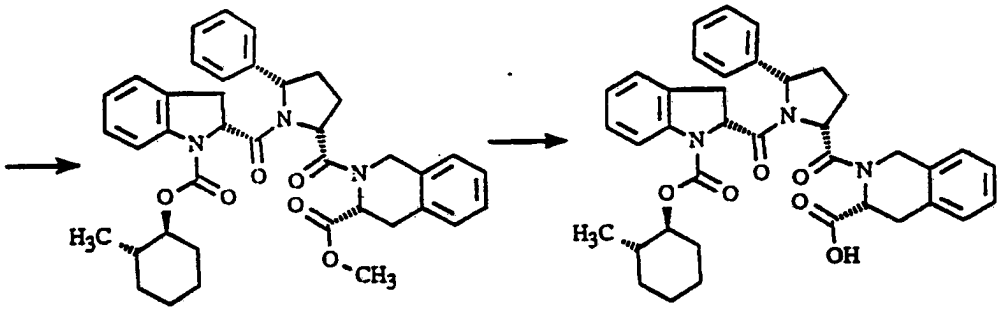
HPLC System A t_R=18.0' >98%

Mass spec (FAB) m/e=636 $[M+H]^+$

EXAMPLE 161



161a 161b



161c 161d

161a Methyl (2R)-1-(2-*trans*-methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carboxylate.

This was prepared from (±)-2-*trans*-methylcyclohexanol on a 1.64 mmol scale following the method described for 157a. The product was isolated in 28% yield after flash chromatography on silica gel (eluant EtOAc:hexane 20:80 v/v).

R_f (EtOAc:hexane 30:70 v/v) 0.41

161b (2R)-1-(2-*trans*-Methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from **161a** on a 0.45 mmol scale following the method described for **1f**. The product was isolated in 44% yield and used without purification.

161c Methyl (3R)-2-{(2R,5S)-1-((2R)-1-(2-*trans*-methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **68a** and **161b** on a 0.20 mmol scale following the method described for **79d**. The product was isolated in 42% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 25:75:1 v/v/v).

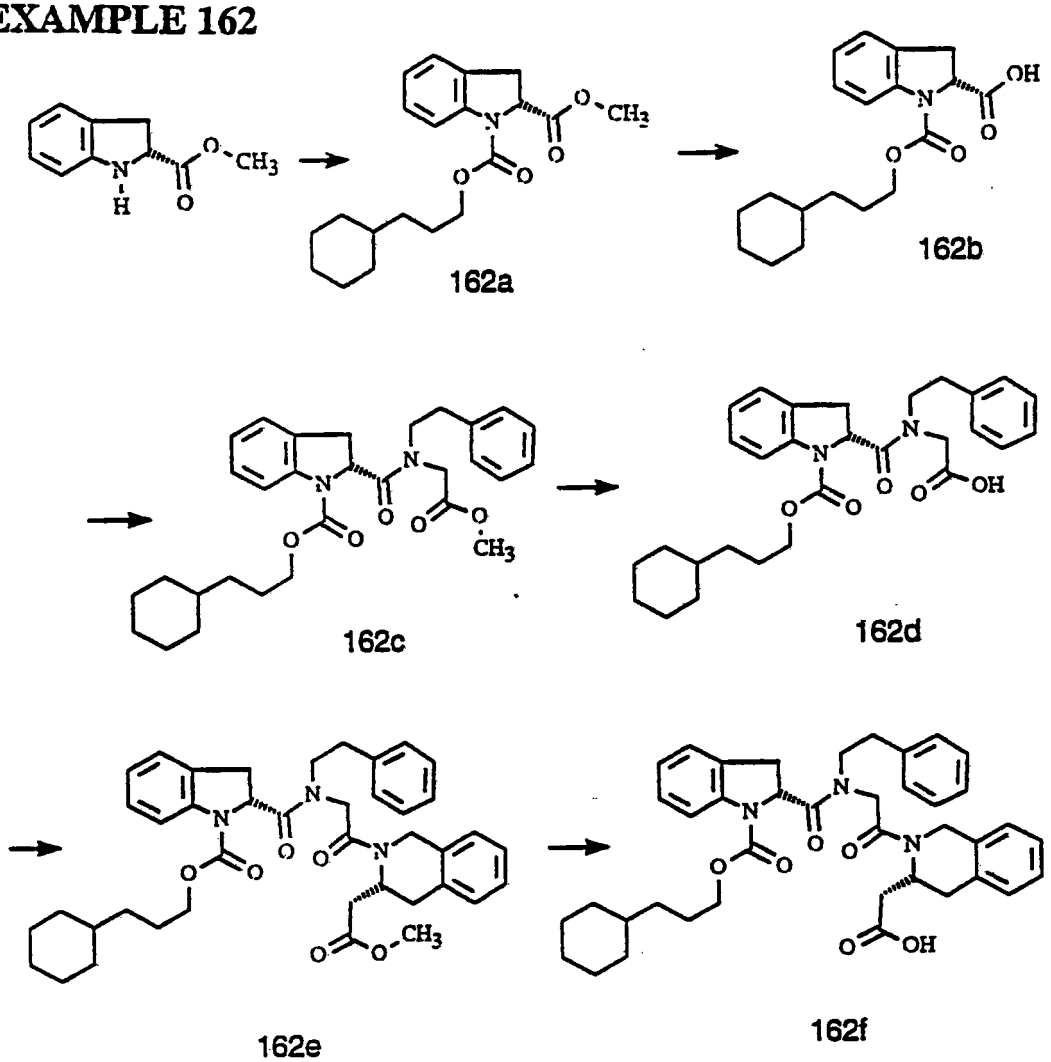
161d (3R)-2-{(2R,5S)-1-((2R)-1-(2-*trans*-Methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **161c** on a 0.08 mmol scale following the method described for **1f**. The product was isolated in 38% yield (20 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 65:35:2 v/v/v).

HPLC System B t_R=18.4' >98%

Mass spec (FAB) m/e=636 $[M+H]^+$

EXAMPLE 162



162a Methyl (2R)-1-(3-cyclohexylpropyl)oxycarbonyl-2.3-dihydroindole-2-carboxylate.

This was prepared from 3-cyclohexylpropanol on a 1.64 mmol scale following the method described for **157a.** The product was isolated in 100% yield after flash chromatography on silica gel (eluant EtOAc:hexane 20:80 v/v).

R_f (EtOAc:hexane 30:70 v/v) 0.49

162b (2R)-1-(3-Cyclohexylpropyl)oxycarbonyl-2.3-dihydroindole-2-carboxylic acid.

This was prepared from **162a** on a 1.64 mmol scale following the method described for **1f.** The product was isolated in 60% yield and used without purification.

162c Methyl N-phenethyl-N-((2R)-1-(3-cyclohexylpropyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.

This was prepared from **32a** and **162b** on a 0.99 mmol scale following the method described for **1d.** The product was isolated in 82% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 35:65:1 v/v/v).

162d N-Phenethyl-N-((2R)-1-(3-cyclohexylpropyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from **162c** on a 0.81 mmol scale following the method described for **1f.** The product was used without purification, assuming a yield of 100%.

162e Methyl (3R)-2-{N-phenethyl-N-((2R)-1-(3-cyclohexylpropyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **1c** and **162d** on a 0.81 mmol scale following the method described for **1d.** The product was isolated in 63% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R_f (EtOAc:hexane 50:50 v/v) 0.34

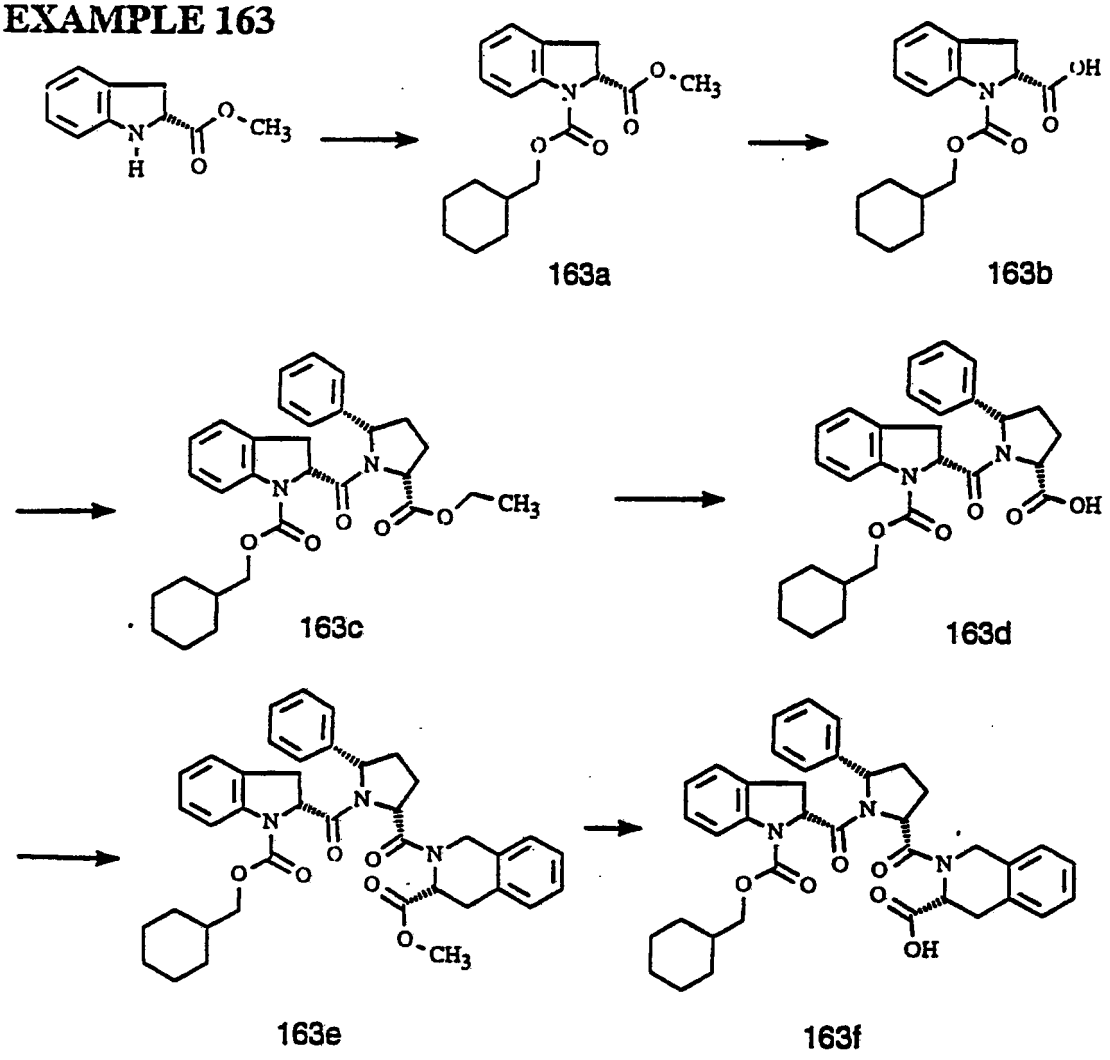
162f (3R)-2-{N-Phenethyl-N-((2R)-1-(3-cyclohexylpropyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **162e** on a 0.51 mmol scale following the method described for **1f.** The product was isolated in 51% yield (161 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 55:45:2 v/v/v).

HPLC System B t_R=21.5' >98%

Mass spec (FAB) m/e=688 $[M+Na]^+$

EXAMPLE 163



163a Methyl (2R)-1-cyclohexylmethyloxycarbonyl-2,3-dihydroindole-2-carboxylate.

This was prepared from cyclohexanemethanol on a 1.64 mmol scale following the method described for **157a**. The product was isolated in 78% yield after flash chromatography on silica gel (eluant EtOAc:hexane 20:80 v/v).

R_f (EtOAc:hexane 30:70 v/v) 0.49

163b (2R)-1-Cyclohexylmethyloxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from **163a** on a 1.27 mmol scale following the method described for **1f**. The product was isolated in 55% yield and used without purification.

163c Ethyl (2R.5S)-1-((2R)-1-cyclohexylmethyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carboxylate.

This was prepared from **30a** and **163b** on a 0.70 mmol scale following the method described for **1d.** The product was isolated in 57% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 25:75:1 v/v/v).

163d (2R.5S)-1-((2R)-1-Cyclohexylmethyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carboxylic acid.

This was prepared from **163c** on a 0.40 mmol scale following the method described for **1f.** The product was used without purification, assuming a yield of 100%.

163e Methyl (3R)-2-{(2R.5S)-1-((2R)-1-cyclohexylmethyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1.2.3.4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **26a** and **163d** on a 0.40 mmol scale following the method described for **1d.** The product was isolated in 64% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R_f (EtOAc:hexane 50:50 v/v) 0.40

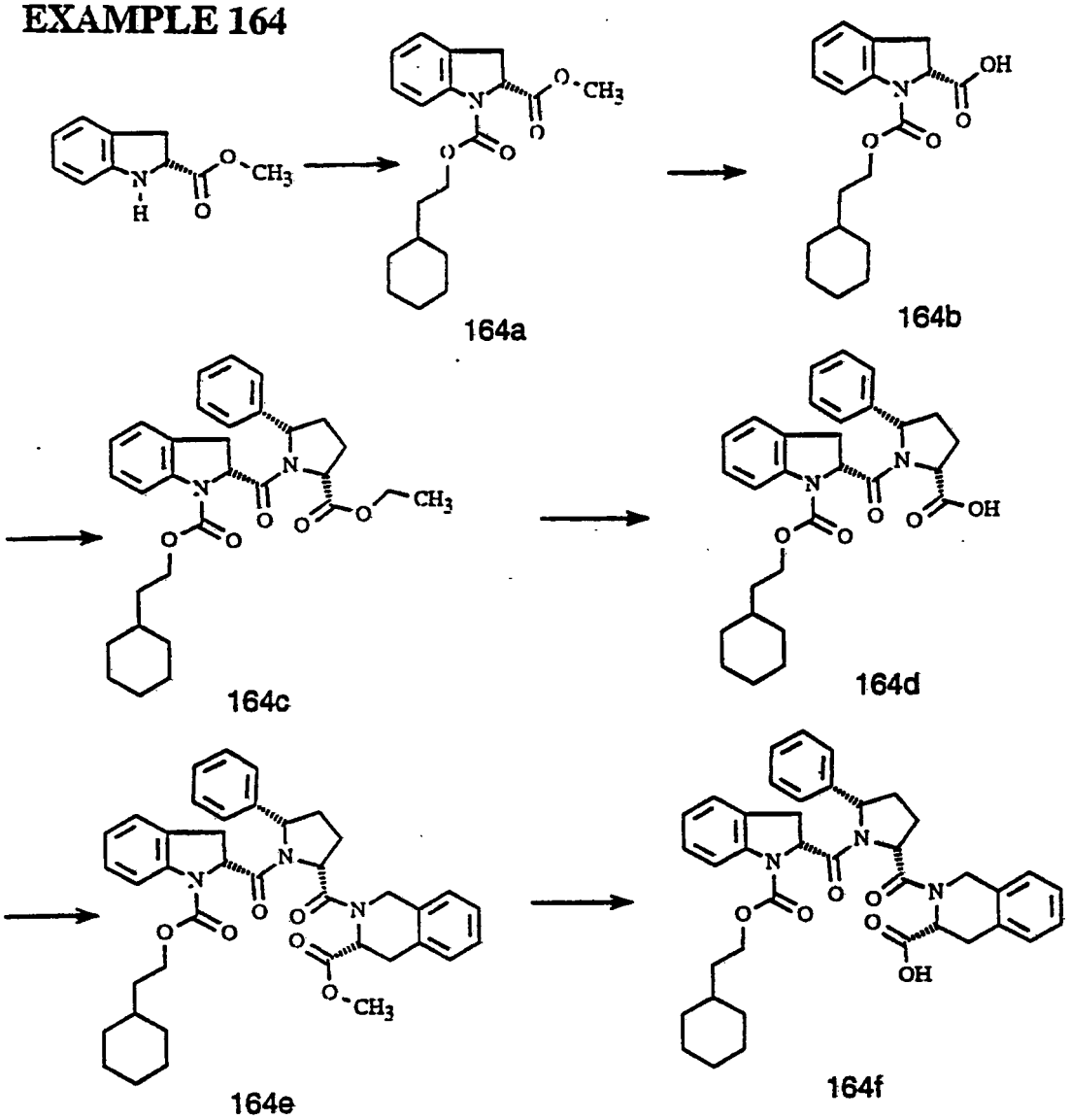
163f (3R)-2-{(2R.5S)-1-((2R)-1-Cyclohexylmethyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1.2.3.4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **163e** on a 0.25 mmol scale following the method described for **1f.** The product was isolated in 16% yield (24 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 50:50:2 v/v/v).

HPLC System B t_R=18.8' >98%

Mass spec (FAB) m/e=636 $[M+H]^+$

EXAMPLE 164



164a Methyl (2R)-1-(2-cyclohexylethyl)oxycarbonyl-2,3-dihydroindole-2-carboxylate.

This was prepared from 2-cyclohexylethanol on a 1.64 mmol scale following the method described for **157a**. The product was isolated in 91% yield after flash chromatography on silica gel (eluant EtOAc:hexane 20:80 v/v).

R_f (EtOAc:hexane 30:70 v/v) 0.54

164b (2R)-1-(2-Cyclohexylethyl)oxycarbonyl-2,3-dihydroindole-2-carboxylic acid.

This was prepared from **164a** on a 1.50 mmol scale following the method described for **1f**. The product was isolated in 55% yield and used without purification.

164c Ethyl (2R,5S)-1-((2R)-1-(2-cyclohexylethyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carboxylate.

This was prepared from **30a** and **164b** on a 0.82 mmol scale following the method described for **1d**. The product was isolated in 56% yield after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 25:75:1 v/v/v).

164d (2R,5S)-1-((2R)-1-(2-Cyclohexylethyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carboxylic acid.

This was prepared from **164c** on a 0.46 mmol scale following the method described for **1f**. The product was used without purification, assuming a yield of 100%.

164e Methyl (3R)-2-{(2R,5S)-1-((2R)-1-(2-cyclohexylethyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from **26a** and **164d** on a 0.46 mmol scale following the method described for **1d**. The product was isolated in 72% yield after flash chromatography on silica gel (eluant EtOAc:hexane 40:60 v/v).

R_f (EtOAc:hexane 50:50 v/v) 0.40

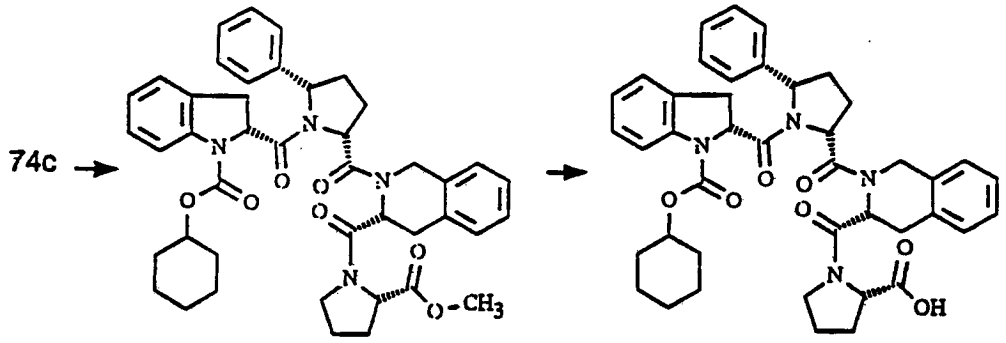
164f (3R)-2-{(2R,5S)-1-((2R)-1-(2-Cyclohexylethyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from **164e** on a 0.33 mmol scale following the method described for **1f**. The product was isolated in 16% yield (33 mg) after flash chromatography on silica gel (eluant EtOAc:hexane:AcOH 50:50:2 v/v/v).

HPLC System B t_R=21.8' >90%

Mass spec (FAB) m/e=650 $[M+H]^+$

EXAMPLE 165



165a 165b

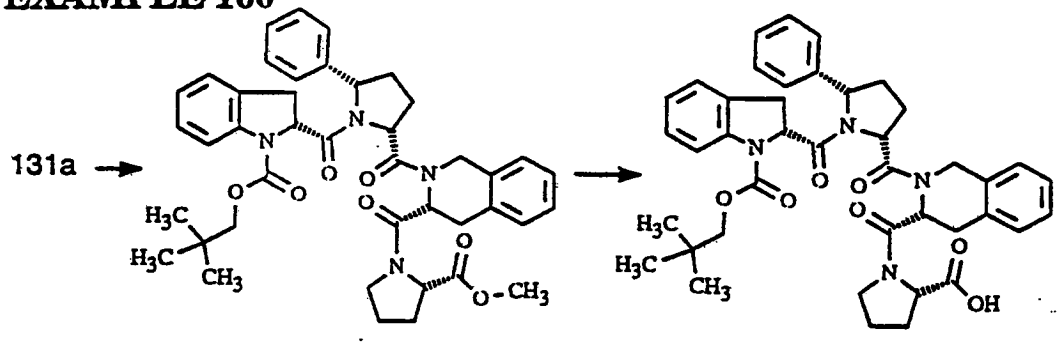
165a Methyl N-{(3R)-2-{(2R.5S)-1-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2.3,4-tetrahydroisoquinoline-3-carbonyl}-prolinate.

This was prepared from 74c and ProOMe on a 0.08 mmol scale following the method described for **1d.** The product was used without purification, assuming a yield of 100%.
R_f (EtOAc:pet. ether 70:30 v/v) 0.22

165b N-{(3R)-2-{(2R.5S)-1-((2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2.3.4-tetrahydroisoquinoline-3-carbonyl}-proline.

This was prepared from **165a** on a 0.08 mmol scale following the method described for **1f.** The product was isolated in 57% yield (31 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:1 v/v).
HPLC System A t_R=15.5' >98%
AAA Peptide content=83%
Mass spec (FAB) m/e=604. 272

EXAMPLE 166



166a 166b

166a Methyl N-{(3R)-2-{(2R.5S)-1-((2R)-1-neopentyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1.2.3.4-tetrahydroisoquinoline-3-carbonyl}-prolinate.

This was prepared from **131a** on a 0.30 mmol scale following the method described for **81a.** The product was isolated in 32% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 50:50 v/v).

166b N-{(3R)-2-{(2R.5S)-1-((2R)-1-Neopentyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1.2.3.4-tetrahydroisoquinoline-3-carbonyl}-proline.

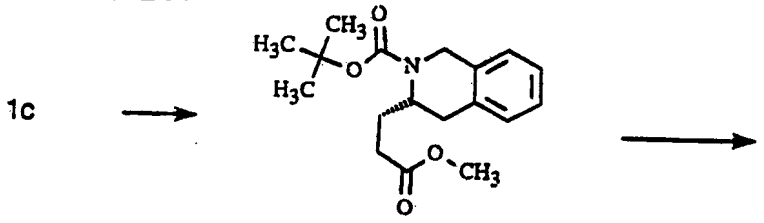
This was prepared from **166a** on a 0.10 mmol scale following the method described for **1f.** The product was isolated in 89% yield (61 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:1 v/v).

HPLC System A t_R=15.1' >98%

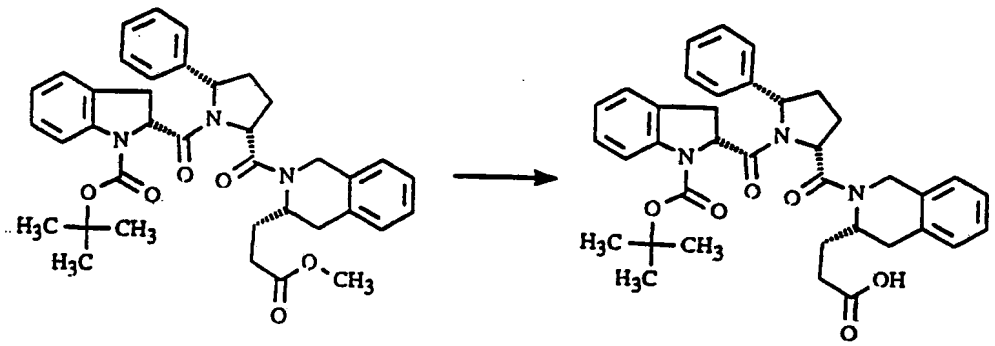
AAA Peptide content=76%

Mass spec (FAB) m/e=592, 272

EXAMPLE 167



167a



167b 167c

167a Methyl (3R)-2-*tert*-butyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-propanoate.

This was prepared from **1b** on a 3.6 mmol scale. The ester was hydrolysed following the method described for **1f** to give the corresponding acid which was then homologated following the method described for **1b**. The intermediate diazoketone was purified by flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v) and the title product was isolated in 22% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 20:80 v/v).

R_f (EtOAc:pet. ether 10:90 v/v) 0.12

^1H NMR δ 1.49 (9H,s); 1.6 - 1.9 (2H,m); 2.3 (2H,m); 2.63 (1H,dd,J=16,2 Hz); 3.09 (1H,dd,J=16,6 Hz); 3.64 (3H,s); 4.2 (1H,br); 4.6 (1H,br); 4.9 (1H,br); 7.0 - 7.2 (4H,m)

167b Methyl (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-propanoate.

This was prepared from **79b** and **167a** on a 0.39 mmol scale following the method described for **79d**. The product was isolated in 71% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

R_f (EtOAc:pet. ether 30:70 v/v) 0.13

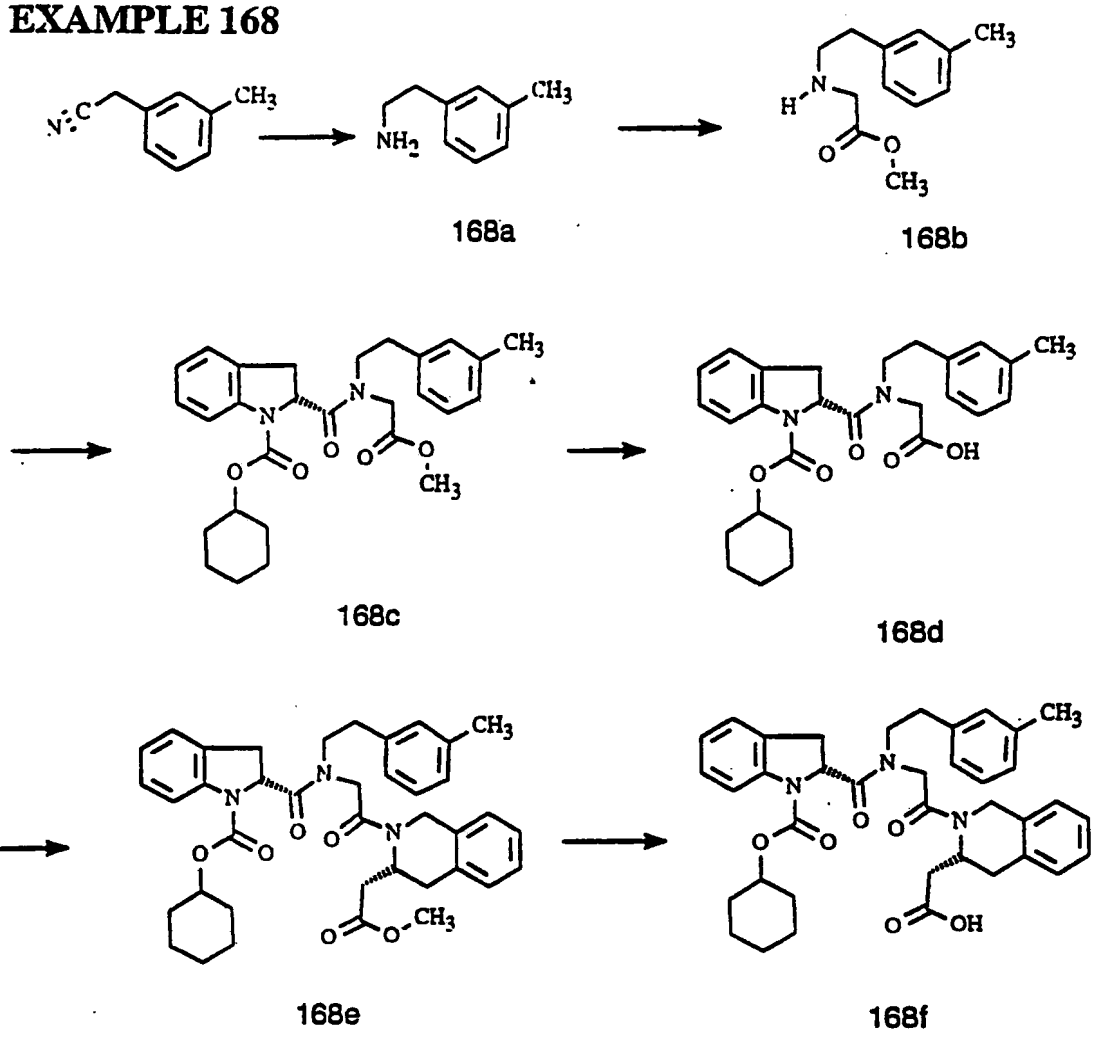
167c (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-propanoic acid.

This was prepared from **167b** on a 0.28 mmol scale following the method described for **1f**. The product was isolated in 74% yield (130 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 55:45:1 v/v/v).

HPLC System A t_R=15.4' >98%

Mass spec (FAB) m/e=624 $[M+H]^+$

EXAMPLE 168



168a 168b 168c 168d 168e 168f

168a 3-Methylphenethylamine.

To a stirred solution of 3-methylbenzyl cyanide (1 g, 7.6 mmol) and $CoCl_2$ (0.49 g, 3.8 mmol) in MeOH (20 mL) was added $NaBH_4$ (1.2 g, 30.4 mmol) portionwise at room temperature. The mixture was stirred for 30 min then poured onto crushed ice. 10% Aq. $KHSO_4$ was added until the mixture was strongly acidic (pH 2), and the insoluble material was removed by filtration through Celite. The filtrate was treated with NaOH pellets until basic (pH 10) and extracted once with EtOAc, then twice with CH_2Cl_2. The separate extracts were washed with brine, dried over Na_2SO_4, combined and evaporated to give the title compound (0.60 g, 59%) which was used without purification.

168b Methyl N-3-methylphenethyl-glycinate.

This was prepared from **168a** on a 4.45 mmol scale following the method described for **32a.** The product was isolated in 6% yield after flash chromatography on silica gel (eluant EtOAc).

168c Methyl N-3-methylphenethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.

This was prepared from **74a** and **168b** on a 0.26 mmol scale following the method described for **1d.** The product was isolated in 69% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

168d N-3-Methylphenethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from **168c** on a 0.18 mmol scale following the method described for **1f.** The product was used without purification, assuming a yield of 100%.

168e Methyl (3R)-2-{N-3-methylphenethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **1c** and **168d** on a 0.18 mmol scale following the method described for **1d.** The product was isolated in 70% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

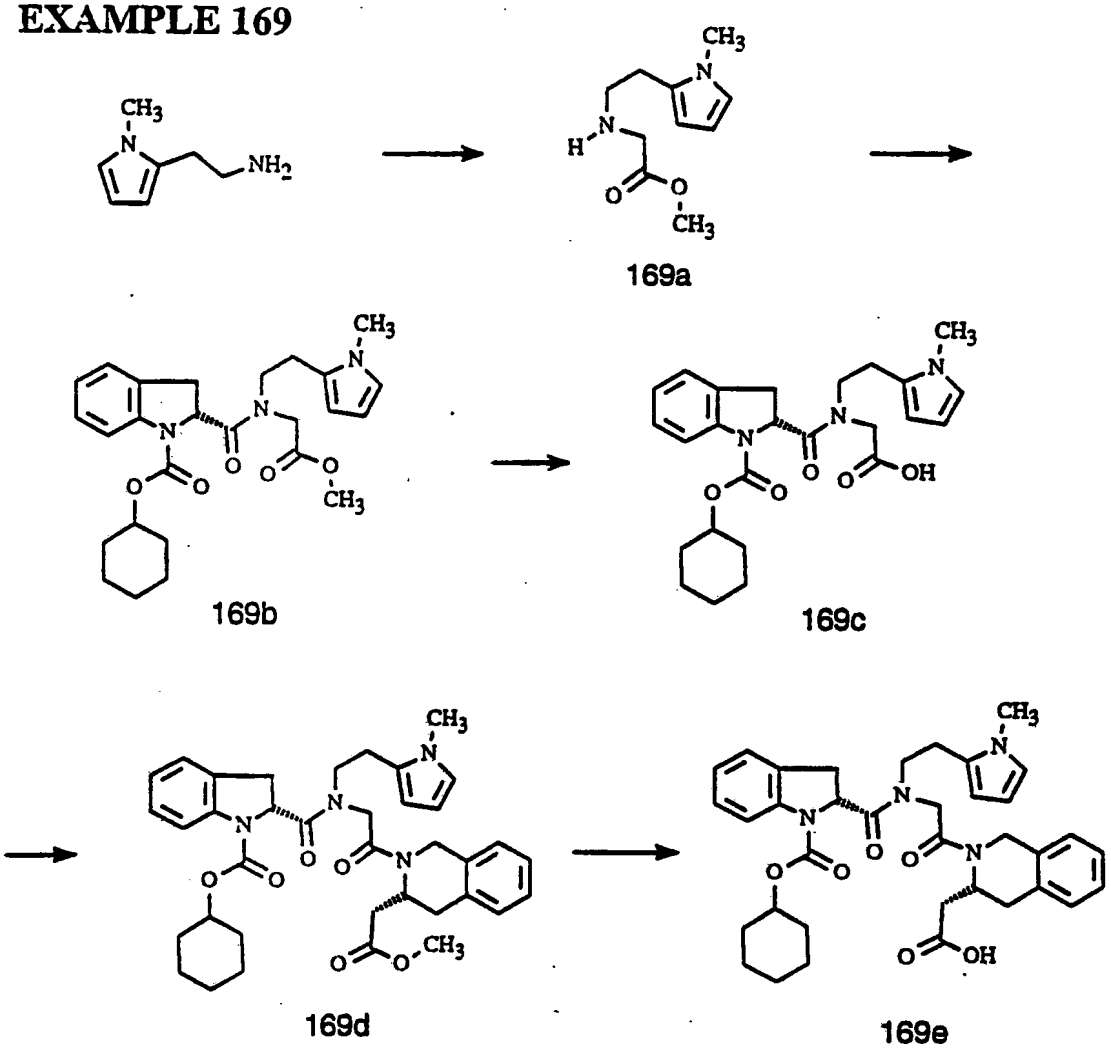
168f (3R)-2-{N-3-Methylphenethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **168e** on a 0.13 mmol scale following the method described for **1f.** The product was isolated in 72% yield (60 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 70:30:1 v/v/v).

HPLC System A t_R=17.1' >98%

Mass spec (FAB) m/e=660 $[M+Na]^+$

EXAMPLE 169



169a

169b

169c

169d

169e

169a Methyl N-(2-(1-Methylpyrrol-2-yl)ethyl)-glycinate.

This was prepared from 2-(1-methylpyrrol-2-yl)ethylamine on a 8.0 mmol scale following the method described for **32a**. The product was isolated in 27% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 70:30 then EtOAc).

169b Methyl N-(2-(1-Methylpyrrol-2-yl)ethyl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.

This was prepared from **74a** and **169a** on a 2.16 mmol scale following the method described for **1d**. The product was isolated in 34% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

169c N-(2-(1-Methylpyrrol-2-yl)ethyl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from **169b** on a 0.73 mmol scale following the method described for **1f**. The product was used without purification, assuming a yield of 100%.

169d Methyl (3R)-2-{N-(2-(1-Methylpyrrol-2-yl)ethyl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **1c** and **169c** on a 0.73 mmol scale following the method described for **1d**. The product was isolated in 58% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

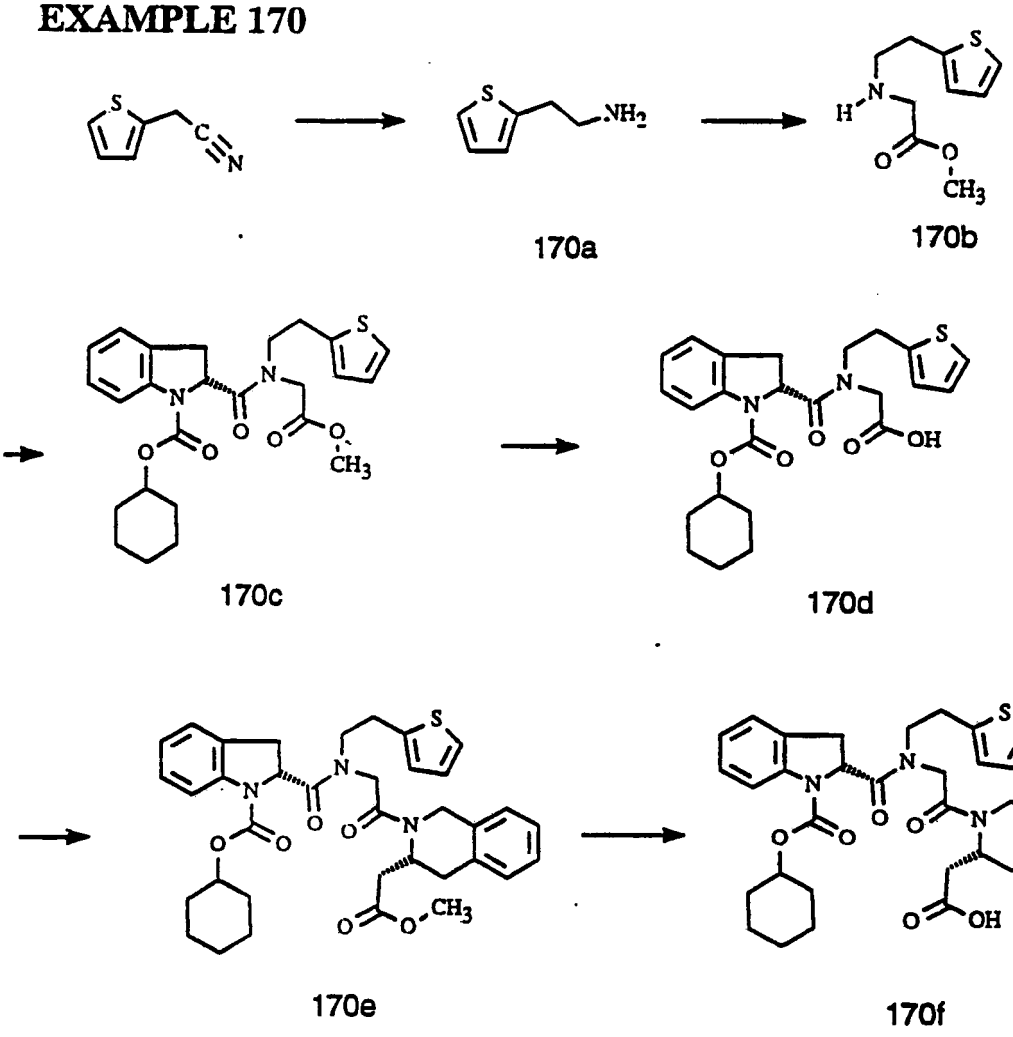
169e (3R)-2-{N-(2-(1-Methylpyrrol-2-yl)ethyl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from **169d** on a 0.42 mmol scale following the method described for **1f**. The product was isolated in 75% yield (197 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 80:20:2 v/v/v).

HPLC System A t_R=15.0' >98%

Mass spec (FAB) m/e=627 $[M+H]^+$

EXAMPLE 170



170a 170b 170c 170d 170e 170f

170a (2-Thienyl)ethylamine.

This was prepared from 2-thienylacetonitrile on an 18.6 mmol scale following the method described for **168a**. The product was isolated in 32% yield and used without purification.

170b Methyl N-(2-thienyl)ethyl-glycinate.

This was prepared from **170a** on a 5.96 mmol scale following the method described for **32a**. The product was isolated in 35% yield after flash chromatography on silica gel (eluant $CHCl_3$:MeOH:AcOH 30:2:1 v/v/v).

170c Methyl N-(2-thienyl)ethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.

This was prepared from **74a** and **170b** on a 1.05 mmol scale following the method described for **1d**. The product was isolated in 71% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

170d N-(2-Thienyl)ethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from 170c on a 0.75 mmol scale following the method described for **1f**. The product was used without purification, assuming a yield of 100%.

170e Methyl (3R)-2-{N-(2-thienyl)ethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from **1c** and **170d** on a 0.75 mmol scale following the method described for **1d**. The product was isolated in 59% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

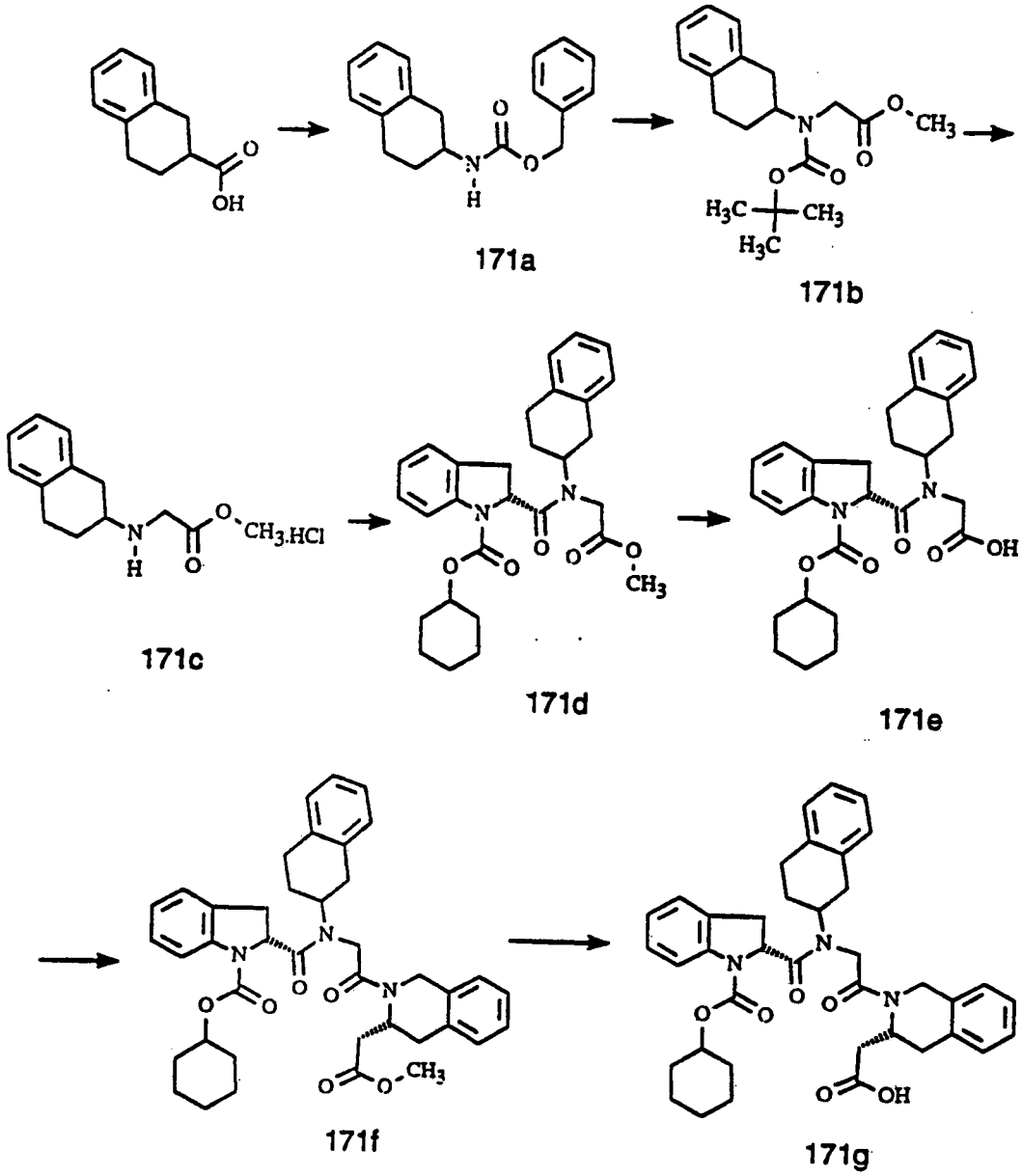
170f (3R)-2-{N-(2-Thienyl)ethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 170e on a 0.44 mmol scale following the method described for **1f**. The product was isolated in 57% yield (157 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 80:20:1 v/v/v).

HPLC System A t_R=14.8' >98%

Mass spec (FAB) m/e=493 $[M+H]^+$

EXAMPLE 171



171a (2RS)-2-Benyloxycarbonylamino-1,2,3,4-tetrahydronaphthalene.

To a stirred solution of 1,2,3,4-tetrahydronaphthalene-2-carboxylic acid (3 g, 17 mmol) and N-methylmorpholine (2.1 mL, 18.7 mmol) under N_2 was added $(PhO)_2P(O)N_3$ (4 mL, 18.7 mmol) and the mixture was heated at reflux for 2.5 hr then cooled to room temperature. Benzyl alcohol (3.7 mL, 34 mmol) was added and the solution was heated at reflux overnight, cooled to room temperature, and concentrated *in vacuo*. The residue was taken up in EtOAc and washed successively with aq. $KHSO_4$, $KHCO_3$ (twice), water and

brine. filtered (Whatman 1PS phase separator) and concentrated. The product was isolated in 57% yield (4.07 g) after flash chromatography on silica gel (eluant EtOAc:pet. ether 10:90 v/v)

171b Methyl N-((2RS)-1,2,3,4-tetrahydronaphth-2-yl)-N-*tert*-butyloxycarbonyl-glycinate.

This was prepared from 171a on a 7.1 mmol scale in three steps. The amine was deprotected by catalytic hydrogenolysis over 5% Pd-on-carbon. then alkylated following the method described for 32a and finally reprotected with BOC_2O following the method described for **141c** (second part). The product was isolated in 14% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 10:90 v/v).

171c Methyl N-((2RS)-1,2,3,4-tetrahydronaphth-2-yl)-glycinate hydrochloride.

This was prepared from 171b on a 1.0 mmol scale following the method described for **1c.** The product was used without purification, assuming a yield of 100%.

171d Methyl N-((2RS)-1,2,3,4-tetrahydronaphth-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycinate.

This was prepared from 74a and **171c** on a 1.0 mmol scale following the method described for **1d.** The product was isolated in 48% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

171e N-((2RS)-1,2,3,4-Tetrahydronaphth-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycine.

This was prepared from 171d on a 0.48 mmol scale following the method described for **1f.** The product was used without purification, assuming a yield of 100%.

171f Methyl (3R)-2-{N-((2RS)-1,2,3,4-tetrahydronaphth-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetate.

This was prepared from 1c and **171e** on a 0.48 mmol scale following the method described for **1d.** The product was isolated in 52% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

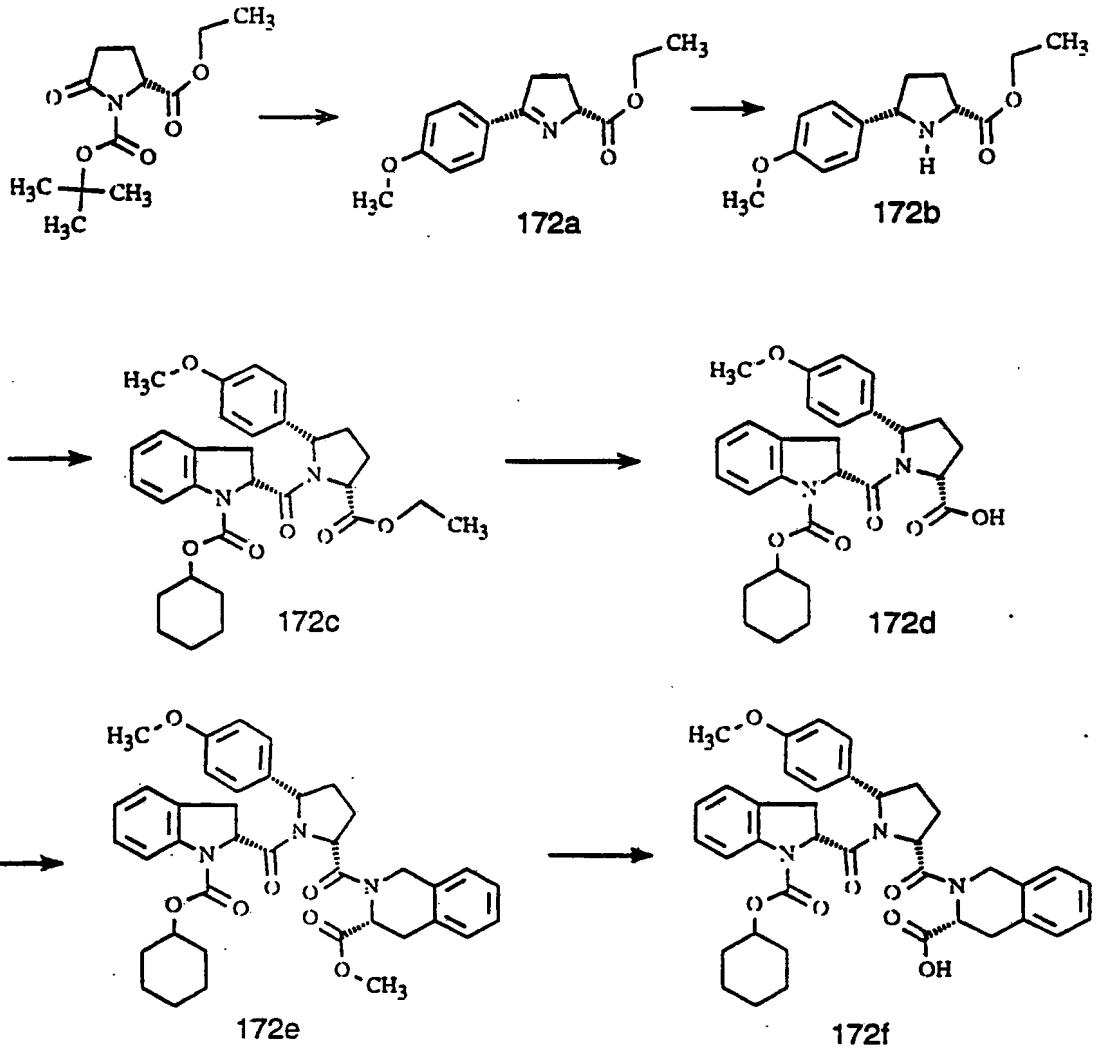
171g **(3R)-2-{N-((2RS)-1.2.3.4-Tetrahydronaphth-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-glycyl}-1.2.3.4-tetrahydroisoquinoline-3-acetic acid.**

This was prepared from 171f on a 0.25 mmol scale following the method described for 1f. The product was isolated in 60% yield (97 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 45:55:1 v/v/v).

HPLC System A t_R=16.8' >95%

Mass spec (FAB) m/e=650 $[M+H]^+$

EXAMPLE 172



172a Ethyl (2R)-3,4-dihydro-5-(4-methoxyphenyl)-2H-pyrrole-2-carboxylate.

This was prepared from 4-methoxyphenylmagnesium bromide on an 8.0 mmol scale following the method described for **87a**. The product was isolated in 82% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 then 40:60 v/v).

172b Ethyl (2R,5S)-5-(4-methoxyphenyl)-pyrrolidine-2-carboxylate.

This was prepared from 172a on a 6.6 mmol scale following the method described for **30a**. The product was isolated in 56% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 then 50:50 v/v).

172c Ethyl (2R,5S)-1-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(4-methoxyphenyl)-pyrrolidine-2-carboxylate.

This was prepared from **74a** and **172b** on a 0.69 mmol scale following the method described for **1d**. The product was isolated in 95% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

172d (2R,5S)-1-((2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(4-methoxyphenyl)-pyrrolidine-2-carboxylic acid.

This was prepared from 172c on a 0.65 mmol scale following the method described for **1f**. The product was used without purification, assuming a yield of 100%.

172e Methyl (3R)-2-{(2R,5S)-1-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(4-methoxyphenyl)-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

This was prepared from 26a and **172d** on a 0.32 mmol scale following the method described for **1d**. The product was isolated in 69% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

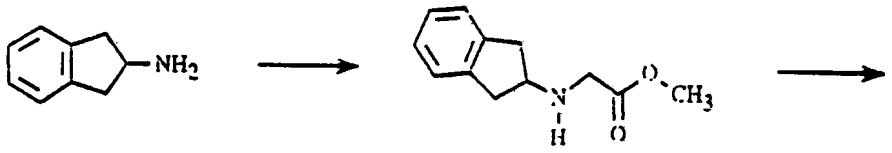
172f (3R)-2-{(2R,5S)-1-((2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(4-methoxyphenyl)-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

This was prepared from 172e on a 0.22 mmol scale following the method described for **1f**. The product was isolated in 69% yield (95 mg) after flash chromatography on silica gel (eluant EtOAc:AcOH 100:2 v/v).

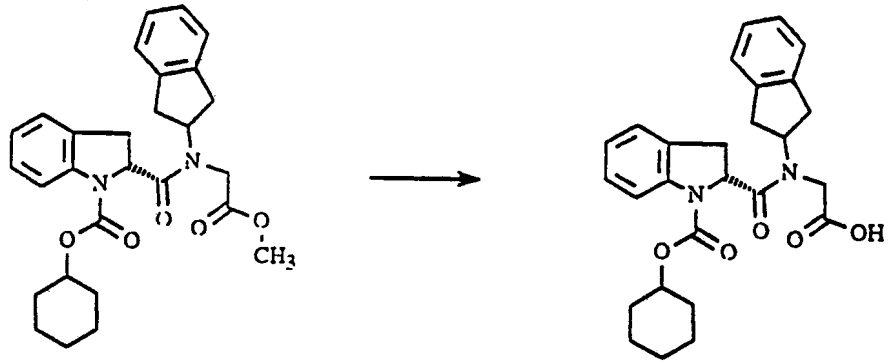
HPLC System A t_R=15.4' >98%

Mass spec (FAB) m/e=652 $[M+H]^+$

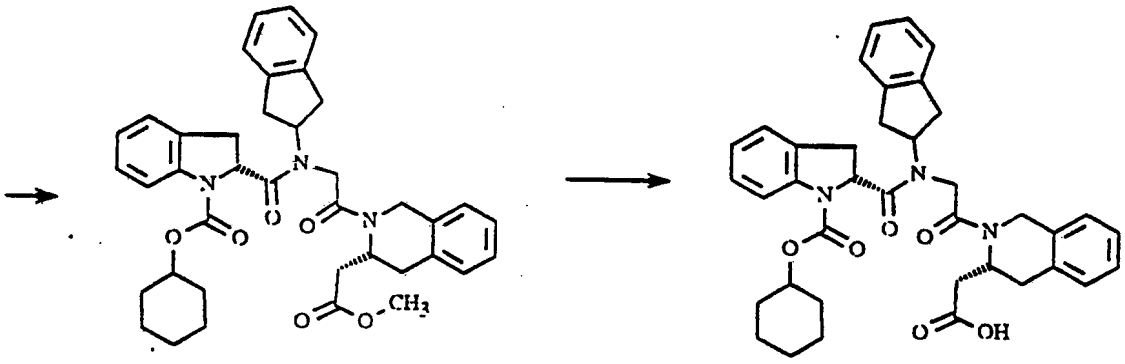
EXAMPLE 173



173a



173b 173c



173d 173e

173a Methyl N-(indan-2-yl)-glycinate.

This was prepared from indan-2-amine on an 8.0 mmol scale following the method described for **32a.** The product was isolated in 44% yield after flash chromatography on silica gel (eluant EtOAc).

173b Methyl N-(indan-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-glycinate.

This was prepared from 74a and 173a on a 0.69 mmol scale following the method described for **1d.** The product was isolated in 80% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 30:70 v/v).

173c N-(Indan-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-glycine.

This was prepared from 173b on a 0.55 mmol scale following the method described for 1f. The product was used without purification, assuming a yield of 100%.

173d Methyl (3R)-2-{N-(indan-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-glycyl}-1.2.3.4-tetrahydroisoquinoline-3-acetate.

This was prepared from 1c and 173c on a 0.27 mmol scale following the method described for **1d.** The product was isolated in 73% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 40:60 v/v).

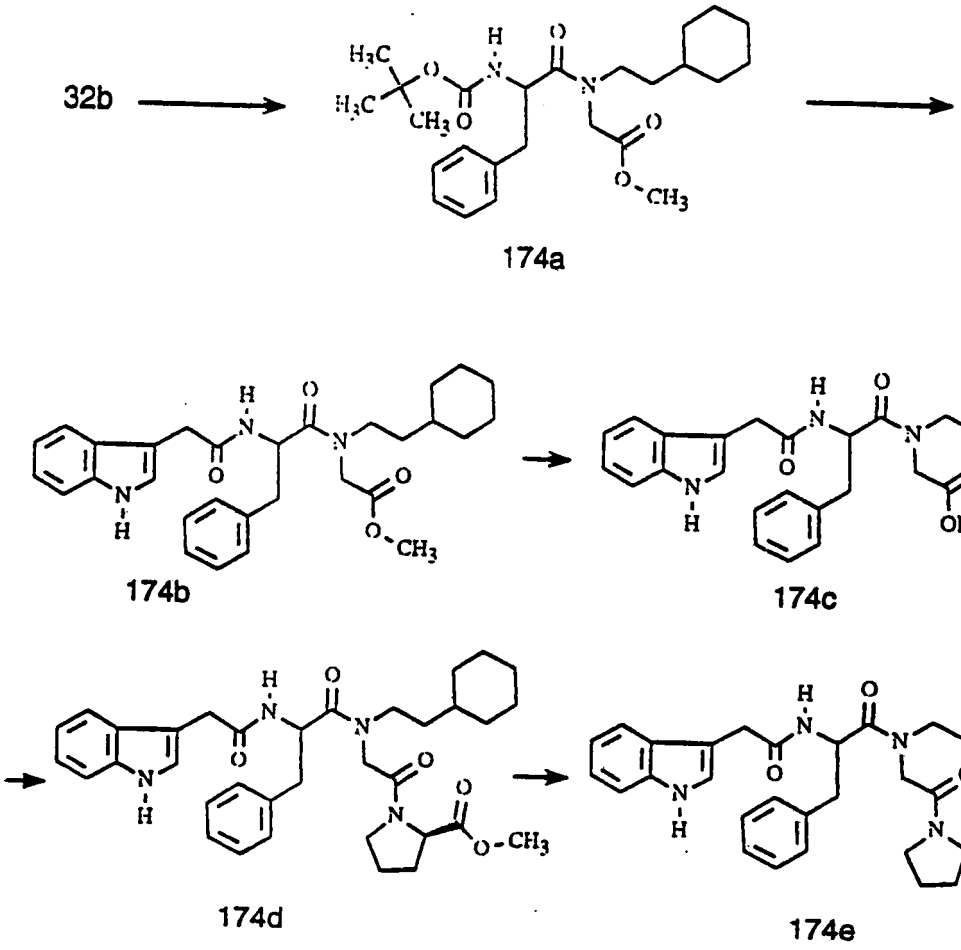
173e (3R)-2-{N-(Indan-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2.3-dihydroindole-2-carbonyl)-glycyl}-1.2.3.4-tetrahydroisoquinoline-3-acetic acid.

This was prepared from 173d on a 0.20 mmol scale following the method described for 1f. The product was isolated in ??% yield (75 mg) after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 80:20:2 v/v/v).

HPLC System A t_R=15.8' >98%

Mass spec (FAB) m/e=658 $[M+H]^+$

EXAMPLE 174



174a Methyl N-(2-cyclohexylethyl)-N-(N-*tert*-butyloxycarbonyl-phenylalanyl)-glycinate.

This was prepared from 32b and BOCPheOH on a 2.0 mmol scale following the method described for **1d**. The product was isolated in 93% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether 25:75 v/v).

174b Methyl N-(2-cyclohexylethyl)-N-(N-(3-indoleacetyl)-phenylalanyl)-glycinate.

This was prepared from **174a** on a 1.86 mmol scale following the method described for **32d**. The product was isolated in 52% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 65:35:1 v/v/v).

174c N-(2-Cyclohexylethyl)-N-(N-(3-indoleacetyl)-phenylalanyl)-glycine.

This was prepared from 174b on a 0.48 mmol scale following the method described for 34. The product was used without purification, assuming a yield of 100%.

174d Methyl 1-{N-(2-cyclohexylethyl)-N-(N-(3-indoleacetyl)-phenylalanyl)-glycyl}-D-prolinate.

This was prepared from 174c and D-ProOMe on a 0.48 mmol scale following the method described for 34. The product was isolated in 42% yield after flash chromatography on silica gel (eluant EtOAc).

174e 1-{N-(2-Cyclohexylethyl)-N-(N-(3-indoleacetyl)-phenylalanyl)-glycyl}-D-proline.

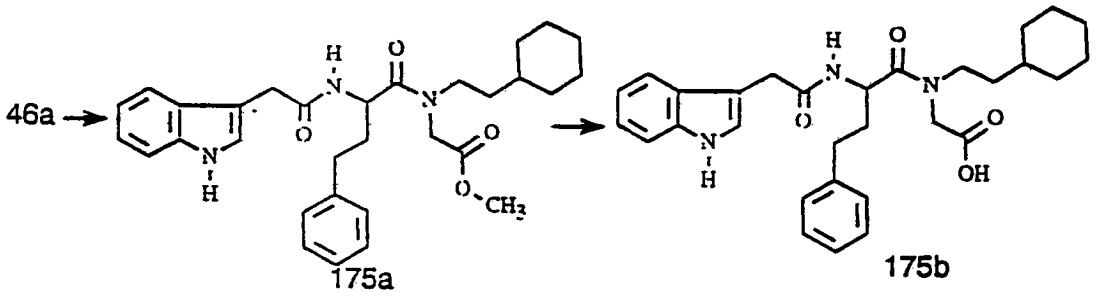
This was prepared from 174d on a 0.20 mmol scale following the method described for 1f. The product was isolated in 61% yield (72 mg) after flash chromatography on silica gel (eluant $CHCl_3$:MeOH:AcOH 35:2:1 v/v/v).

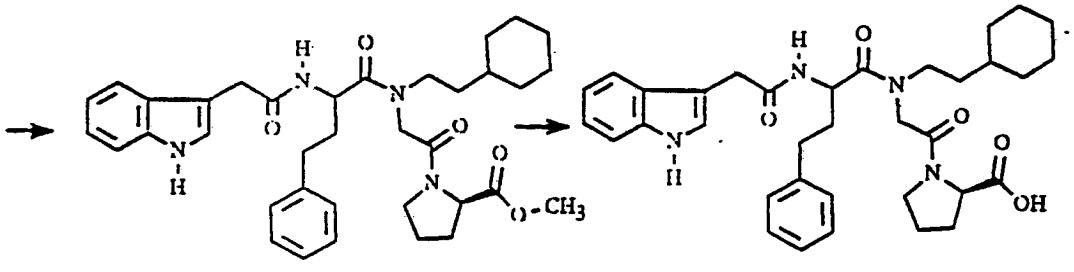
HPLC System B t_R=10.4' >95%

AAA Phe 0.98: Pro 1.02: Peptide content=87%

Mass spec (FAB) m/e=587 $[M+H]^+$

EXAMPLE 175





175a Methyl N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-4-phenylbutanoyl)-glycinate.

This was prepared from 46a on a 1.74 mmol scale following the method described for **32d.** The product was isolated in 61% yield after flash chromatography on silica gel (eluant EtOAc:pet. ether:AcOH 65:35:1 v/v/v).

175b N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-4-phenylbutanoyl)-glycine.

This was prepared from 175a on a 0.53 mmol scale following the method described for **1f.** The product was used without purification, assuming a yield of 100%.

175c Methyl 1-{N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-4-phenylbutanoyl)-glycyl}-D-prolinate.

This was prepared from 175b and D-ProOMe on a 0.53 mmol scale following the method described for **34.** The product was isolated in 39% yield after flash chromatography on silica gel (eluant EtOAc).

175d 1-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-4-phenylbutanoyl)-glycyl}-D-proline.

This was prepared from 175c on a 0.29 mmol scale following the method described for **1f.** The product was isolated in 67% yield (116 mg) after flash chromatography on silica gel (eluant $CHCl_3$:MeOH:AcOH 35:2:1 v/v/v).
HPLC System B t_R=15.8' >98%
AAA Hph 1.04; Pro 0.96; Peptide content=93%
Mass spec (FAB) m/e=623 $[M+Na]^+$

BIOLOGICAL TESTING

The compounds of the present invention are potent ligands for the CCK-A and/or CCK-B receptors. Those which are antagonists at the CCK-B receptor also inhibit gastric acid secretion stimulated by pentagastrin. The methods for measuring these activities are described below:

Measurement of binding affinity for CCK-A receptors

The pancreas of an SD rat was homogenized in a 20-fold volume of 50 mM Tris-HCl buffer (pH 7.7) by the use of a Polytrone-type homogenizer. the homogenate was twice centrifuged for 10 minutes at 50000 g by the use of an ultra-centrifuge. the precipitate thus obtained was suspended in a 40-fold volume of 50 mM Tris-HCl buffer (containing 0.2% BSA. 5 mM $MgCl_2$. 0.1 mg/ml bacitracin and 5 mM DTT: pH 7.7). and the suspension was stored at -80°C until the membrane preparations were required.

The membrane preparations were then warmed to room temperature, diluted 1:10 with the buffer and incubated at 37°C for 30 minutes in the presence of [^{3}H]L-364.718 and the test compound then separated by suction filtration. Non-specific binding was determined in the presence of 1 μM L-364.718. The amount of labelled ligand bound to the receptor was measured by the use of a liquid scintillation counter; IC_{50} values were determined. being that concentration of test compound required to inhibit specific binding by 50%.

Measurement of binding affinity for CCK-B receptors

About 100 SD rats were decapitated without anaesthesia. the whole brain was immediately excised from each of the rats and homogenized in 10-fold volume of 0.32 M aqueous solution of sucrose by the use of a Teflon-coated homogenizer. the homogenate thus obtained was centrifuged for 10 minutes at 900 g by the use of a cooled centrifuge, and the supernatant was further centrifuged for 15 minutes at 11500 g. The precipitate thus obtained was dispersed in 50 mM Tris-HCl buffer (pH 7.4) containing 0.08% Triton X-100. this suspension was allowed to stand for 30 minutes and again centrifuged for 15 minutes at 11500 g. the precipitate thus obtained was washed twice with 5 mM Tris-HCl buffer and twice with 50 mM Tris-HCl buffer in that order with centrifugal separation. the washed precipitate was suspended in 50 mM Tris-HCl buffer. and the suspension thus obtained was stored at -80°C until the membrane preparation was required.

The membrane preparations were warmed to room temperature. diluted with 10 mM HEPES buffer (containing 130 mM. NaCl. 5 mM $MgCl_2$. 1mM EGTA and 0.25 mg/ml bacitracin; pH 6.5) and incubated at 25°C for 120 minutes in the presence of [^{125}I]BH-CCK-8 and the test compound. then separated by suction filtration. Non-specific binding was determined in the presence of 1 μM CCK-8. The amount of labelled ligand bound to the receptor was measured by the use of a γ-counter; IC_{50} values were determined. being that concentration of test compound required to inhibit specific binding by 50%.

Table 1 summarises CCK-A and CCK-B binding data for representative examples of the preferred compounds:

Table 1

Example No.	Receptor binding affinity IC_{50} (nM)	
	CCK-A	CCK-B
1	170	20
2	160	10
3	430	43
11	>10.000	760
16	7.700	480
17	10.000	270
18	6.500	390
19	3.500	290
21	>10.000	140
24	>10.000	190
28	4.7	22
30	5.600	100
31	2.700	18
36	>10.000	2.3
45	>10.000	30
69	>10.000	39
74	>10.000	1.0
75	>10.000	0.87
85	>10.000	9.0
89	>10.000	1.9
97	>10.000	16
107	>10.000	56
127	>10.000	800
131	>10.000	0.25
136	>10.000	20
141	>10.000	4.7
146	>10.000	9.3
152	>10.000	2.9
153	>10.000	1.0

Table 1 (cont.)

Example No.	Receptor binding affinity IC_{50} (nM)	
	CCK-A	CCK-B
160	>10.000	8.8
165	>10.000	1.0
171	>10.000	8.7
174	>10.000	0.94

Measurement of inhibition of pentagastrin-stimulated gastric acid secretion in rat

A cannula was inserted into the trachea of a rat anaesthetised with urethane (intraperitoneally administered, 1.25 g/Kg), its abdominal wall was incised to expose the gastric and duodenal portions, and a polyethylene cannula was set in the anterior stomach after ligation of the cardia. The duodenum was then subjected to slight section, a polyethylene cannula was inserted from the incised portion toward the stomach, and the pylorus was ligated to fix the cannula.

Physiological saline (with pH adjusted to 7.0) was perfused from the anterior stomach toward the pylorus at a rate of 3 ml/min, and the gastric-acid secretion was measured by continuous titration of the perfusate by the use of a pH-stat (AUT-201; product of Toa Electronics, Ltd.). The continuous titration was carried out by using 25 mM NaOH solution until the pH reached 7.0, and the result was expressed as the amount of gastric acid secreted for every 10 minutes (mE_q/10 min.). Pentagastrin was intravenously administered at a rate of 15 μg/Kg/hr.

The secretion of gastric acid increased upon administration of pentagastrin, reaching the maximum level after 60 minutes and stably maintaining this level after that. A test drug was then intravenously administered, and the secretion of gastric acid was measured: ED_{50} values were determined, being the amount of the drug required to reduce the amount of secreted gastric acid down to 50% of the maximum level.

Table 2 illustrates representative ED_{50} values. It can be seen that compounds of the present invention show a substantial advantage over previously reported gastrin antagonists.

Table 2

	ED_{50} (μmol/kg)
Compound of Example 281 of US Patent No. 4.820,834 (L-365,260)	4.2
Compound of Example 20 of European Patent No. 0.405,537 A1 (PD-134308)	2.1
Compound of Example 74	0.74
Compound of Example 153	0.20

The experiments described above demonstrate that the compounds of the present invention are high affinity ligands for the CCK-A and/or the CCK-B receptor, and that those which preferentially bind to the CCK-B receptor can inhibit the stimulation of gastric acid release due to pentagastrin. They are therefore useful in the treatment of disease states in which the CCK-A, CCK-B or gastrin receptor is implicated as a mediating factor.

In the case of the CCK-A receptor such disease states would include pancreatitis, disorders of gastrointestinal motility, irritable bowel syndrome, and CCK-dependent tumours.

In the case of the CCK-B receptor such disease states would include disorders of the central nervous system such as anxiety, psychoses, Parkinson's disease, Tourette's syndrome, Huntingdon's chorea, and neural damage following ischaemia (for example after a stroke).

In the case of the gastrin receptor such disease states would include disorders of the gastro-intestinal system, for example gastric and duodenal ulceration, gastritis, reflux esophagitis, Zollinger-Ellison syndrome, gastrin-sensitive pancreatitis, and gastrin-sensitive tumors.

The compounds of the invention can also be used in the control of appetite and pain (including the potentiation of opiate analgesia).

The compounds of this invention and salts thereof can be administered orally (including sublingual administration) or parenterally in the form of tablets, powders, capsules, pills, liquids, injections, suppositories, ointments and adhesive plasters.

The carrier and excipient for pharmaceutical manufacturing can be a solid or liquid, nontoxic medicinal substance, such as lactose, magnesium stearate, starch, talc, gelatin, agar, pectin, gum arabic, olive oil, sesame oil, cocoa butter, ethylene glycol and other commonly employed materials.

Examples of formulations using the compounds of this invention are described below.

Preparation of 20 mg-tablets

Compound of Example 4 (100 g), lactose (367 g) and corn starch (90g) were homogeneously mixed together by the use of a flow granulating coater (product of Ohgawara Seisakusho), 10% aqueous solution of hydroxypropylcellulose (200 g) was sprayed into the mixture, and granulation was then performed. After drying, the granules were filtered through a 20-mesh sieve, 20 g of carboxymethylcellulose Ca and 3 g of magnesium stearate were then added, and the mixture was treated in a rotary tablet machine equipped with a pestle of 7 mm x 8.4 R (product of Hata Tekkosho), thus producing tablets each weighing 120 mg.

Preparation of 40 mg-tablets

Compound of Example 4 (140 g), lactose (280 g) and corn starch (70g) were homogeneously mixed together by the use of a flow granulating coater (product of Ohgawara Seisakusho), 10% aqueous solution of hydroxypropylcellulose (175 g) was sprayed into the mixture, and granulation was then performed. After drying, the granules were filtered through a 20-mesh sieve, 14.7 g of carboxymethylcellulose Ca and 2.8 g of magnesium stearate were then added, and the mixture was treated in a rotary tablet machine equipped with a pestle of 7.5 mm x 9R (product of Hata Tekkosho), thus producing tablets each weighing 150 mg.

The clinical dosage of the compounds of this invention will be determined by the physician taking into account the precise illness, and the body weight, age, sex, medical history and other factors of the patient to be treated. In general the dosage when administered orally will be between 1 and 1000 mg/day in either a single dose or sub-divided into smaller multiple doses.

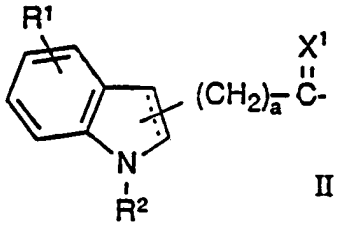
CLAIMS

1. Compounds of general formula I. or pharmaceutically acceptable salts thereof:

A - B - C I

wherein:

A is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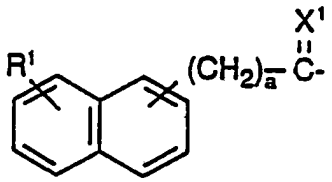
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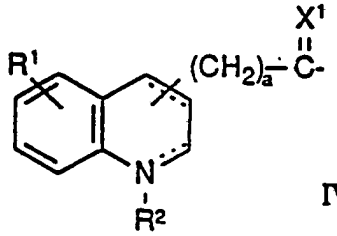
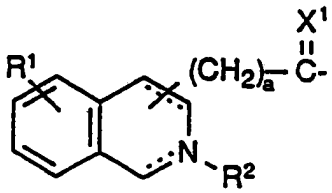

IV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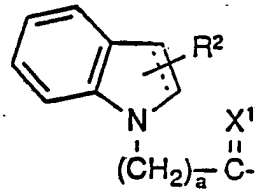
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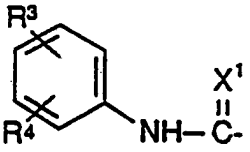
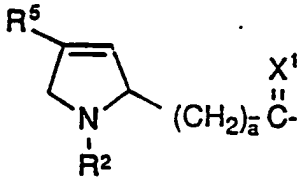
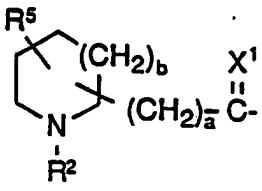
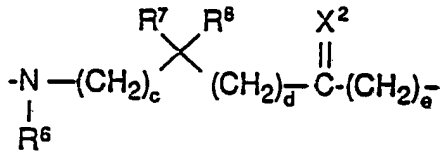

VII


VIII

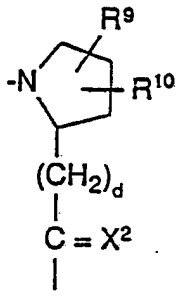

IX

or an α-amino acid residue containing an aromatic side-chain (e.g. L-Trp, L-Hph, L-Phe, L-Phg, D-Trp, D-Hph, D-Phe, D-Phg) which is optionally substituted at the N-terminal amino group; the N-terminal substituent is selected from R^2.

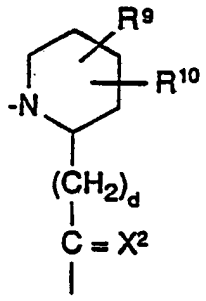
B is



X



XI



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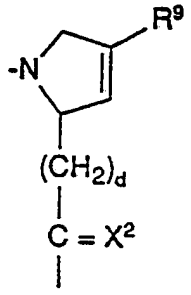
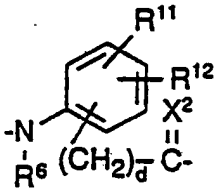
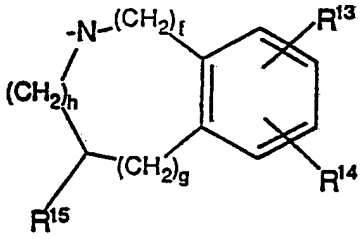


XIII

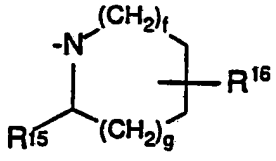


XIV

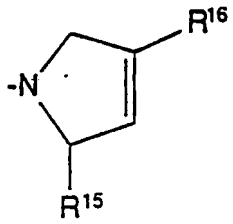
C is



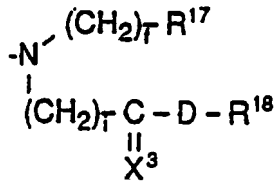
XV



XVI

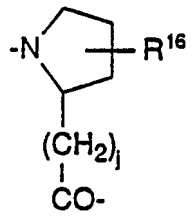


XVII

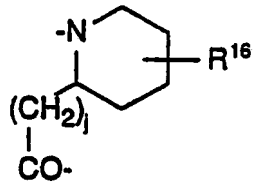


XVIII

D (in the exemplifications of C showing it) is absent, any α-amino or imino acid residue, any N-methylated α-amino acid residue, β-alanine;



XIX



XX

R^1 is -H, halo, -OH, $-CO_2H$, $-CF_3$, $-NO_2$, -CN, CH_3, lower alkoxy (C_1 - C_3, linear or branched), lower alkylcarbonyl (C_1 - C_3, linear or branched), phenylcarbonyl;

R^2 is absent, H, alkyl (C_1 - C_{10}, linear, branched or cyclic), unsubstituted or substituted phenylmethyl (substituents are 1 or 2 of halo, -OH, $-CO_2H$, $-CF_3$, $-NO_2$, -CN, $-CH_3$, or $-OCH_3$), $-CSR^{19}$, $-COR^{19}$, $-CO_2R^{19}$, $-CONR^{19}R^{20}$, $-CH_2CO_2R^{19}$, $-CH_2COR^{19}$, $-SO_2R^{19}$;

R^3 and R^4 are independently selected from R^1, but when situated on adjacent carbons may form an unsubstituted fused aromatic carbocyclic or heterocyclic ring;

R^5 is H, -OH, lower alkyl (C_1 - C_6, linear or branched) lower alkoxy (C_1 - C_6, linear or branched), substituted or unsubstituted phenyl or phenylmethyl or phenylmethoxy (substituents are 1 or 2 of halo, $-CH_3$, $-OCH_3$, $-CO_2H$, $-NO_2$, $-CF_3$ or -OH), cyclohexyl, cyclohexylmethyl, cyclohexylmethoxy;

R^6 is H, $-(CH_2)_k-X^4-(CH_2)_l-R^{21}$, 1-indanyl, 2-indanyl, 1,2,3,4-tetrahydronaphth-1-yl, or 1,2,3,4-tetrahydronaphth-2-yl;

R^7 is H, methyl, or together with R^8 forms a saturated, unsubstituted, cycloalkyl ring (C_3 - C_6);

R^8 is H, tert-butyl, cycloalkyl (C_3 - C_8), substituted or unsubstituted phenyl (substituents are 1 or 2 of halo, -CN, $-CH_3$, $-OCH_3$, $-CO_2H$, $-NO_2$, $-CF_3$ or -OH), the side chain of a naturally occurring α-amino acid, $-CHR^{22}R^{23}$, or together with R^7 forms a saturated unsubstituted cycloalkyl ring (C_3 - C_6);

R^9 and R^{10} are independently selected from R^5, phenylthio, phenoxy, 1-napthyl, 2-napthyl, or when situated on adjacent carbons may together form a fused benzene ring;

R^{11} and R^{12} are independently H, halo, -OH, $-NO_2$, $-CO_2H$, $-CF_3$, $-CH_3$, $-OCH_3$, phenyl, or together when on adjacent carbons R^{11} and R^{12} may form a second benzene ring;

R^{13} and R^{14} are independently chosen from H, halo, -OH, $-NO_2$, $-CF_3$, $-CH_3$, $-OCH_3$, $-(CH_2)_mCO_2H$, $-(CH_2)_mCONH_2$, $-(CH_2)_mCO_2CH_3$, $-(CH_2)_mSO_3H$, or together when situated on adjacent carbons R^{13} and R^{14} may form a second fused benzene ring;

R^{15} is H, lower alkyl (C_1 - C_6, linear or branched), substituted or unsubstituted phenyl or phenylmethyl (substituents are 1 or 2 of halo, $-CH_3$, $-OCH_3$, $-CO_2H$, $-NO_2$, $-CF_3$, -CN or -OH); or

XXI XXII

where the double bond may be either of cis or trans disposition:

R^{16} is defined as R^5;

R^{17} is H, di-lower alkyl (C_1 - C_4) methyl, cycloalkyl (C_3 - C_{10}), -O-cycloalkyl (C_3 - C_{10}), -S-cycloalkyl (C_3 - C_{10}), $-SO_2$-cycloalkyl (C_3 - C_{10}), -1-adamantyl, -2-adamantyl, unsubstituted or substituted phenyl (substituents are 1 or 2 of halo, $-CH_3$, $-OCH_3$, $-CO_2H$, $-NO_2$, $-CF_3$ or -OH);

R^{18} is -H, -OH, $-CO_2H$, $-CO_2CH_3$, alkyl (C_1 - C_6, linear or branched), cycloalkyl (C_3 - C_7), alkoxy (C_1 - C_6, linear or branched), phenylmethyl, phenylmethoxy, $NR^{24}R^{25}$;

R^{19} and R^{20} are independently selected from H, alkyl (C_1 - C_{12}, linear or branched), cycloalkyl (C_3 - C_8)-$(CH_2)_n$- or polycycloalkyl (C_3 - C_{12})-$(CH_2)_n$- where said cyclic or said polycyclic group may be further substituted by up to four substituents independently selected from C_1 - C_3 alkyl; substituted or unsubstituted phenyl-$(CH_2)_n$- (substitutents may be 1 or 2 from halo, $-CH_3$, $-OCH_3$, $-CO_2H$, $-NO_2$, $-CF_3$ or -OH), 1-adamantyl, 2-adamantyl, heterocycloalkyl (3-8 membered ring, where heteroatoms are 1 or 2 of $-NR^{26}$-, -O-, -S-, $-SO_2$-), or together R^{19} and R^{20} in combination with the N of an $NR^{19}R^{20}$ group may form a 3-8 membered heterocyclic ring;

R^{21} is branched alkyl (C_3 - C_8), cycloalkyl (C_3 - C_8), unsubstituted or substituted phenyl (substituents are 1 or 2 of halo, $-CF_3$, $-CO_2H$, alkyl (C_1 - C_5, linear or branched), alkoxy (C_1 - C_5, linear or branched), -CN, $-NO_2$ and -OH), 1- or 2-napthyl, 2- or 3-indolyl; 2-, 3- or 4-pyridyl; 2- or 3-thienyl; 1-, 2- or 3-pyrrolyl; 2- or 3-(1-methyl)pyrrolyl; 2- or 3-furyl;

R^{22} and R^{23} are independently H, alkyl (C_1 - C_8, linear or branched),

$-(CH_2)_o-X^5-(CH_2-)_pR^{27}$,
$-(CH_2)_o-CO_2R^{27}$,
$-(CH_2)_o-R^{27}$,
$-(CH_2)_o-CONR^{28}R^{29}$,
$-OCO(CH_2)_o-R^{27}$,
$-OCONH(CH_2)_o-R^{27}$,
$-NHCO_2(CH_2)_o-R^{27}$;

R^{24} and R^{25} are independently H, alkyl (C_1 - C_6, linear or branched), or together with the N of the $NR^{24}R^{25}$ group form an unsubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring;

R^{26} is H, lower alkyl (C_1 - C_4, linear or branched), phenyl or phenylmethyl;

R^{27} is H, alkyl (C_3 - C_6, linear or branched), cycloalkyl (C_3 - C_8), substituted or unsubstituted phenyl or phenylmethyl (substituents are 1 or 2 of halo, $-CH_3$, $-OCH_3$, $-CO_2H$, $-NO_2$, $-CF_3$ or -OH), 1-adamantyl, 2-adamantyl;

R^{28} and R^{29} are independently R^{27} or together with the N of the $NR^{28}R^{29}$ group form an unsubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring, or benzofused 4-7 membered heterocyclic ring;

and wherein:

a is 0 - 3
b is 0 - 2
c is 0 or 1
d is 0 - 2
e is 0 or 1
f is 0 - 4
g is 0 - 3
h is 0 - 2
i is 0 - 3
j is 0 - 2
k is 0 - 3
l is 0 - 3
m is 0 - 3
n is 0 - 4
o is 0 - 3
p is 0 - 3
q is 0 - 4
X^1 is O, H_2, S
X^2 is O, H_2, S
X^3 is O, H_2, S, F_2
X^4 is absent, -O-, -CHOH-, -CO-, $-SO_2-$
X^5 is absent, $-O(CH_2)_q-$, $-(CH_2)_q-CO-$,
$-O(CH_2)_q-CO-$, $-S-(CH_2)_q-$, $-SO_2(CH_2)_q-$,
$-SO_2(CH_2)_q-CO-$, $-SO(CH_2)_q-$, $-NH(CH_2)_q-$,
$-NCH_3(CH_2)_q-$, $-NH(CH_2)_qCO-$, $NCH_3(CH_2)_qCO-$.

$\equiv$ can be either a single or double bond; when two occur in the same molecule they must be simultaneously double or single.

2. Compounds of Claim 1 or pharmaceutically acceptable salts thereof, wherein:

A is VII
B is X, XIV
C is XV, XVI or XVII

3. Compounds of Claim 2 or pharmaceutically acceptable salts thereof, wherein:

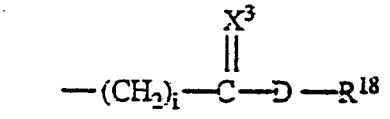
B is X
C is XV
R^3 is at the 3- position of the aryl ring
R^4 is H
R^6 is H or CH_3
R^7 is H or CH_3

and wherein:

c + d + e= 0 or 1
f is 0 or 1
g is 0, 1 or 2
h is 0 or 1
X^1 is O
X^2 is O or H_2

4. Compounds of Claim 3 or pharmaceutically acceptable salts thereof, wherein:

R^6 is H;
R^7 is H;
R^8 is tert-butyl, cycloalkyl (C_3 - C_8), substituted or unsubstituted phenyl (substituents are 1 or 2 of halo, alkyl (C_1 - C_3), alkoxy (C_1 - C_3), -CO_2H, -NO_2, -CF_3 or -OH), $CHR^{22}R^{23}$;
R^{13} is H, halo, -CH_3, -OCH_3;
R^{14} is H;

R^{15} is  XXI

wherein D is absent, Gly or β-Ala;

R^{18} is -OH, lower alkyl (C_1 - C_4, linear or branched), lower alkoxy (C_1 - C_4, linear or branched), $NR^{24}R^{25}$;

R^{22} and R^{23} are independently H, lower alkyl (C_1 - C_6, linear or branched), lower alkoxy (C_1 - C_4, linear or branched)

$-(CH_2)_o-X^5-(CH_2)_p-R^{27}$
$-(CH_2)_o-R^{25}$

R^{24} and R^{25} are independently H, methyl, ethyl or in combination with the N of the $NR^{22}R^{23}$ group together form an unsubstituted, saturated or unsaturated, 4-7 membered heterocyclic ring;

c is 0
d is 0
e is 0 or 1
i is 0 or 1
X^3 is O or H_2

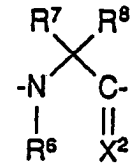
5. Compounds of Claim 4 or pharmaceutically acceptable salts thereof, wherein:

R^3 is -Cl, -Br, $-CH_3$ or $-OCH_3$
R^{13} is H
R^{15} is $-(CH_2)_i-CO_2H$
R^{22} and R^{23} are independently lower alkyl (C_1 - C_6, linear or branched), $-(CH_2)_o-O-(CH_2)_p-Ph$, $-(CH_2)_o-Ph$.

e is 0
f is 1
g is 1
h is 0

stereochemistry at R^{15} substituent is R.

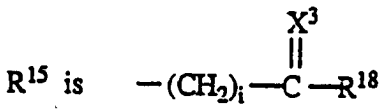
6. Compounds of Claim 2 or pharmaceutically acceptable salts thereof, wherein:

B is  XXIII

(X where c = d = e = zero)

C is XVI or XVII

R^6 and R^7 are independently H or CH_3;

R^{15} is  XXIV

(XXI when D is absent)

R^{16} is phenyl, phenylmethyl, phenylmethoxy, cyclohexyl, cyclohexylmethyl, cyclohexylmethoxy;

R^{18} is -H, -OH, $-NR^{24}R^{25}$, lower alkoxy (C_1 - C_3);

R^{24} and R^{25} are independently H, lower alkyl (C_1 - C_4, linear or branched), or together with the N of the $NR^{22}R^{23}$ group form an unsubstituted, saturated, 4-7 membered heterocyclic ring;

f + g = 1 or 2
i is 0, 1 or 2
X^1 is O
X^2 and X^3 are independently O or H_2.

7. The following particular compounds within claims 2 to 6 or pharmaceutically acceptable salts thereof:

Example No.

1 (3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

2 (3R)-2-[N-(3-Bromophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

3 (3R)-2-[N-(3-Methylphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

4 (3R)-2-[N-(3-Acetylphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

5 (3R)-2-[N-(3-Isopropoxyphenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

6 (3R)-2-[N-(3-Cyanophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

7 (3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-*tert*-butyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

8 (3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-benzoyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

9 (3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-(4-chlorobenzyl)-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

10 (3R)-2-[(2S)-2-(3-Trifluoromethylphenylcarbamoylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

11 (3R)-2-[(2S)-2-(3-Chlorophenylcarbamoylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

12 (3R)-2-[(2S)-2-(N-(3-Chlorophenylcarbamoyl)-methylamino)-hexanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

13 (3R)-2-[(2S)-2-(3,4-Dichlorophenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

14 (3R)-2-[(2S)-2-(2-Methylphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

15 (3R)-2-[(2S)-2-(4-Methylphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

16 (3R)-2-[(2S)-2-(3-Methoxyphenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

Example No.

17 (3R)-2-[(2S)-2-(3-Chlorophenylcarbamoylamino)-4-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

18 (3R)-2-[N-(3-Chlorophenylcarbamoyl)-valyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

19 (3R)-2-[N-(3-Bromophenylcarbamoyl)-valyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

20 (3R)-2-[N-(3-Methylphenylcarbamoyl)-isoleucyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

21 (3R)-2-[(2S)-2-(3-Chlorophenylcarbamoylamino)-3,3-dimethylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

22 (3R)-2-[(S)-α-(3-Chlorophenylcarbamoylamino)-phenylacetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

23 (3R)-2-[(S)-α-(3-Methylphenylcarbamoylamino)-cyclohexaneacetyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

24 (3R)-2-[(2S)-3-(2-Adamantyloxycarbonylamino)-2-(phenylcarbamoylamino)-propanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

25 (3R)-2-[(2S,3R)-2-(3-Chlorophenylcarbamoylamino)-3-phenylbutanoyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

26 (3R)-2-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

27 (3R)-2-[N-(3-Bromophenylcarbamoyl)-O-benzyl-threonyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

28 (2R,4S)-1-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-4-phenylpyrrolidine-2-carboxylic acid.

29 (2R,4R)-1-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-4-phenylpyrrolidine-2-acetic acid.

30 (2R,5S)-1-[N-(3-Chlorophenylcarbamoyl)-O-benzyl-threonyl]-5-phenylpyrrolidine-2-carboxylic acid.

31 (3R)-2-[(2S,3R)-3-Benzyloxy-2-(3-chlorophenylcarbamoylamino)-butyl]-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

8. Compounds of Claim 1 or pharmaceutically acceptable salts thereof, wherein:

A is II, III, IV, V or VI

B is X

C is XVIII

and wherein:

R^1 is H, -OH, halo, $-CH_3$, $-OCH_3$, -CN, $-CO_2H$ or CF_3;

R^2 is absent, H, alkyl (C_1 - C_6, linear or branched), -CO-alkyl (C_1 - C_6, linear or branched), $-CO_2$-alkyl (C_1 - C_6, linear or branched);

R^6 is H, or alkyl (C_1 - C_6, linear or branched);

R^7 is H;

c is 0

X^2 and X^3 are independently H_2 or O.

9. Compounds of Claim 8 or pharmaceutically acceptable salts thereof, wherein:

D (in the exemplifications of C showing it) is absent, Gly, β-Ala, XIX or XX;

and wherein:

R^1 is H;

R^2 is absent or H;

R^6 is H

R^8 is H, the side chain of a naturally occurring α-amino acid, $CHR^{22}R^{23}$;

R^{18} is -OH, $-OCH_3$, $NR^{24}R^{25}$;

R^{22} and R^{23} are independently H, alkyl (C_1 - C_8, linear or branched), $-(CH_2)_o-X^5-(CH_2)_p-R^{27}$, $-(CH_2)_o-CO_2R^{27}$ or $(CH_2)_o-R^{27}$;

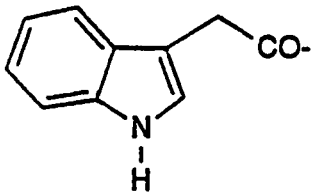
R^{24} and R^{25} are independently H or alkyl (C_1 - C_4, linear or branched), or together with the N of the $NR^{24}R^{25}$ group form an unsubstituted, saturated, 4-7 membered heterocyclic ring;

R^{27} is H, branched alkyl (C_3 - C_6), cycloalkyl (C_3 - C_8), phenyl, 1-adamantyl, 2-adamantyl;

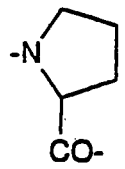
a is 0-2
d and e are 0
f is 1-3
i is 1 or 2

---- are all double bonds.

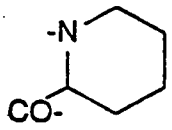
10. Compounds of Claim 9 or pharmaceutically acceptable salts thereof, wherein:

A is  XXV

(II where ---- is a double bond, $R^1 = R^2 = H$, a = 1, $X^1 = O$)

D is absent,  XXVI

(XIX where R^{16} is H, j = zero)

 XXVII

(XX where R^{16} is H, j = zero)

and wherein:

R^{17} is cycloalkyl (C_5 - C_8);

R^{22} is H;

R^{23} is alkyl (C_1 - C_8, linear or branched), $-(CH_2)_o-R^{27}$.

11. The following particular compounds within Claims 9 and 10 or pharmaceutically acceptable salts thereof:

Example No.

32 Methyl N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycinate.

33 N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycine.

34 1-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-pyrrolidine.

35 Methyl N-{N-(2-cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-prolinate.

36 N-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-proline.

37 N-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-pipecolic acid.

38 N-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-glycine.

39 1-{N-(2-Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-pyrrolidine.

40 1-{N-(2-Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-proline.

41 1-{N-(2-Cyclohexylmethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-proline.

42 1-{N-(Cyclooctylmethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-proline.

43 1-{3-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-amino}-propanoyl}-pyrrolidine.

44 N-(3-Cyclohexylpropyl)-N-((2S)-2-(2-indolecarbonylamino)-hexanoyl)-glycine.

45 N-(3-Cyclohexylpropyl)-N-(N-(3-indoleacetyl)-phenylalanyl)-glycine.

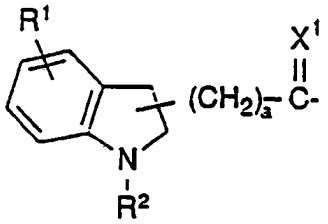
46 N-(2-Cyclohexylethyl)-N-((2S)-2-(3-isoquinolinecarbonylamino)-4-phenylbutanoyl)-glycine.

47 N-{N-Phenethyl-N-((2S)-2-(3-indoleacetylamino)-hexanoyl)-glycyl}-D-proline.

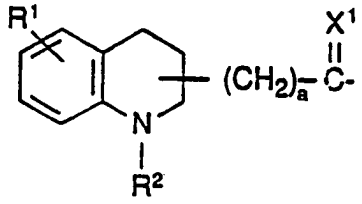
174 1-{N-(2-Cyclohexylethyl)-N-(N-(3-indoleacetyl)-phenylalanyl)-glycyl}-D-proline.

175 1-{N-(2-Cyclohexylethyl)-N-((2S)-2-(3-indoleacetylamino)-4-phenylbutanoyl)-glycyl}-D-proline.

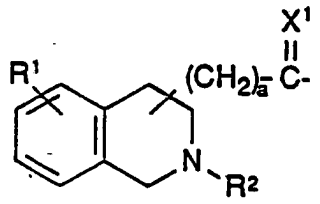
12. Compounds of Claim 1 or pharmaceutically acceptable salts thereof, wherein:

A is IX,  XXVIII

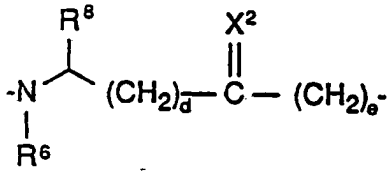
(II where ---- is a single bond)

 XXIX

(IV where ---- are single bonds)

 XXX

(V where ---- are single bonds)

B is  XXXI

(X, where R^7 is H and c is zero)

XI, XII, XIII and XIV

C is XV

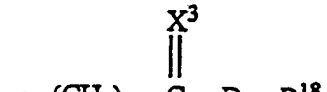
13. Compounds of Claim 12 or pharmaceutically acceptable salts thereof, wherein:

R^1 is H, halo, $-CH_3$ or $-OCH_3$.

R^8 is H or $CHR^{22}R^{23}$ or phenyl.

R^{11} and R^{12} are independently H or phenyl, or together when on adjacent carbons R^{11} and R^{12} may form a second fused aromatic ring, yielding a napthyl moiety.

R^{13} is H.

R^{15} is H, or  XXI

R^{18} is $-OH$, $-OCH_3$ or $-NH_2$;

R^{22} and R^{23} are independently H, alkyl (C_1 - C_4, linear or branched), $-(CH_2)_o-X^5-(CH_2)_p-R^{27}$, $-(CH_2)_o-R^{27}$;

R^{27} is cycloalkyl (C_3 - C_8), phenyl;

and wherein:

a is 0 or 1

d is 0 or 1

e is 0

f is 0 - 2

g is 0 - 2

i is 0 - 2

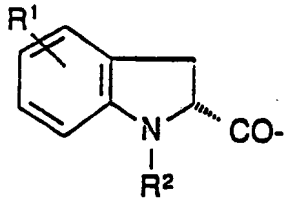
X^1 is O or H_2

X^2 is O or H_2

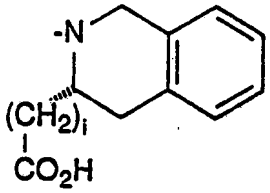
X^3 is O or H_2

X^5 is absent or -O-

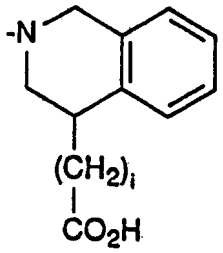
14. Compounds of Claim 13 or pharmaceutically acceptable salts thereof. wherein:

A is  XXXII

(XXVIII with a = zero and X^1 = O);

C is  XXXIII

(XV where f is 1, g is 1, h is 0, R^{13} and R^{14} are H, and R^{15} is -$(CH_2)_iCO_2H$),

 XXXIV

(XV were f is 1, g is 0, h is 1, R^{13} and R^{14} are H, and R^{15} is -$(CH_2)_iCO_2H$);

R^2 is -CO_2R^{19};

R^9 and R^{10} are independently R^5, phenylthio, phenoxy, 1-napthyl or 2-napthyl;

and wherein:

i + j = 0 - 4

X^4 is absent or -CO-.

15. The following particular compounds covered by Claims 12 to 14, or pharmaceutically acceptable salts thereof:

Example No.

48 (3R)-2-{N-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-O-benzyl-threonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

49 (3R)-2-{(2S)-2-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonylamino)-4-phenylbutanoyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

50 (2R)-1-{(2S)-2-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetic acid.

51 (3R)-2-{((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-valyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

52 (3R)-2-{((2R)-1-*tert*-Butylacetyl-2,3-dihydroindole-2-carbonyl)-valyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

53 (3R)-2-{((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-valyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

54 (3R)-2-{((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-isoleucyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

55 (3R)-2-{(S)-α-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonylamino)-phenylacetyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

56 (3R)-2-{((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-D-prolyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

57 (3R)-2-{(2R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-2,3-dihydroindole-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

58 (3R)-2-{(2R,3S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-3-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

59 (3R)-2-{(2R,4S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyi)-4-phenylthio-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

60 (3R)-2-{(2R,4S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenylthio-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

61 (3R)-2-{(2R,4R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenylthio-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

Example No.

62 (3R)-2-{(2R,4R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-benzyloxy-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

63 (3R)-2-{(2R,4R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenoxy-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

64 (3R)-2-{(2R,4R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

65 (3R)-2-{(2R,4S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

66 (3R)-2-{(2R,4S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-benzyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

67 2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline.

68 Methyl (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.

69 (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

70 (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxamide.

71 N-{(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carbonyl}-glycine.

72 (3R)-2-{(2R,5S)-1-((2R)-1-Neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

73 (3R)-2-{(2R,5S)-1-((2R)-1-Isopropyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

74 (3R)-2-{(2R,5S)-1-((2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

Example No.

75 (3R)-2-{(2R,5S)-1-((2R)-1-(2-Adamantyi)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

76 (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butylcarbamoyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

77 (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butylacetyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

78 (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

79 N-{(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetyl}-proline.

80 N-{(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetyl}-D-proline.

81 (3R)-2-{(2R,5S)-1-((2R)-1-Neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

82 (3R)-2-{(2R,5S)-1-((2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

83 (3R)-2-{(2R,5S)-1-((2R)-1-(2-Adamantyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

84 (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-carboxylic acid.

85 (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-acetic acid.

86 (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-benzyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

Example No.

87 (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(2-naphthyl)-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

88 (3R)-2-{(2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

89 (3R)-2-{(2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

90 (3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

91 (3R)-2-{N-3-Phenylpropyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

92 (3R)-2-{N-Benzyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

93 (3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

94 (3R)-2-{N-3-Phenylpropyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

95 (3R)-2-{3-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-amino}-propanoyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

96 (3R)-2-{N-Phenethyl-N-((2R)-1-benzyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

97 (3R)-2-{N-Phenethyl-N-((2R)-1-neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

98 (3R)-2-{N-Phenethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

99 (3R)-2-{N-3-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

100 (3R)-2-{N-(2-Oxo-2-phenylethyl)-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

101 (3R)-2-{N-(2-(3-Indolyl)ethyl)-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

Example No.

102 (3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-carboxylic acid.

103 (3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[*f*]isoquinoline-3-acetic acid.

104 (3R)-2-{N-Pivaloyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-methyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

105 (3R)-2-{3-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonylamino)-naphthalene-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

106 (3R)-2-{3-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonylamino)-naphthalene-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

107 (3R)-2-{(2R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-4-phenyl-2,5-dihydropyrrole-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

108 (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-methyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

109 (3R)-2-{(2S)-2-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-acetylamino)-4-phenylbutanoyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

131 N-{(3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carbonyl}-proline.

132 N-{(3R)-2-{(2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carbonyl}-proline.

133 N-{(3R)-2-{(2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carbonyl}-D-proline.

134 (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-benzyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

135 (3R)-2-{N-2-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

Example No.

136 (3R)-2-{N-4-Chlorophenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

137 (3R)-2-{N-2-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

138 (3R)-2-{N-3-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

139 (3R)-2-{N-4-Methoxyphenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

140 (3R)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydro-benz[h]isoquinoline-3-carboxylic acid.

141 (4RS)-2-{N-Phenethyl-N-((2R)-1-*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-4-acetic acid.

142 (4RS)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-4-acetic acid.

143 (3R)-2-{(2R,5S)-1-((2R)-1-Cyclobutyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

144 (3R)-2-{(2R,5S)-1-((2R)-1-Cyclopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

145 (3R)-2-{(2R,5S)-1-((2R)-1-Cyclopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

146 (3R)-2-{(2R,5S)-1-((2R)-1-(2-*exo*-Norbornyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

147 (3R)-2-{(2R,5S)-1-((2R)-1-Cyclododecyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

Example No.

148 (3R)-2-{N-Phenethyl-N-((2R)-1-*n*-propyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

149 N-{(3R)-2-{(2S,5R)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetyl}-proline.

150 (3R)-2-{N-2-(2-Methoxyphenyl)ethyl-N-((2R)-1-(*tert*-butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxlic acid.

151 (3R)-2-{(2R,5S)-1-((2R)-1-(3,3-Dimethylbutyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

152 (3R)-2-{(2R,5S)-1-((2R)-1-Cycloheptyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

153 (3R)-2-{(2R,5S)-1-((2R)-1-((1S)-*endo*-Bornyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

154 (3R)-2-{(2R,5S)-1-((2R)-1-((1R,2R,3R,5S)-Isopinocampheyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

155 (3R)-2-{(2R,5S)-1-((2R)-1-((1S,2S,3S,5R)-Isopinocampheyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

156 (3R)-2-{(2R,5S)-1-((2R)-1-(3,3-Dimethylbutyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

157 (3R)-2-{(2R,5S)-1-((2R)-1-(1-Piperidino)carbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

158 (3R)-2-{(2R,5S)-1-((2R)-1-(N-Cyclohexyl-N-methylcarbamoyl)-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

159 (3R)-2-{(2R,5S)-1-((2R)-1-(4-*tert*-Butylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

Example No.

160 (3R)-2-{(2R,5S)-1-((2R)-1-(2-*cis*-Methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxyiic acid.

161 (3R)-2-{(2R,5S)-1-((2R)-1-(2-*trans*-Methylcyclohexyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

162 (3R)-2-{N-Phenethyl-N-((2R)-1-(3-cyclohexylpropyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

163 (3R)-2-{(2R,5S)-1-((2R)-1-Cyclohexylmethyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

164 (3R)-2-{(2R,5S)-1-((2R)-1-(2-Cyclohexylethyl)oxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

165 N-{(3R)-2-{(2R,5S)-1-((2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carbonyl}-proline.

166 N-{(3R)-2-{(2R,5S)-1-((2R)-1-Neopentyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-carbonyl}-proline.

167 (3R)-2-{(2R,5S)-1-((2R)-1-*tert*-Butyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-phenyl-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-propanoic acid.

168 (3R)-2-{N-3-Methylphenethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

169 (3R)-2-{N-(2-(1-Methylpyrrol-2-yl)ethyl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

170 (3R)-2-{N-(2-Thienyl)ethyl-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

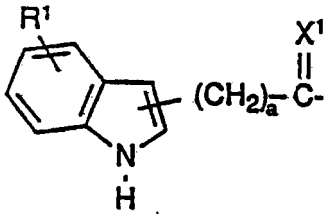
Example No.

171 (3R)-2-{N-((2RS)-1,2,3,4-Tetrahydronaphth-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

172 (3R)-2-{(2R,5S)-1-((2R)-1-Cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-5-(4-methoxyphenyl)-pyrrolidine-2-carbonyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

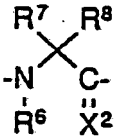
173 (3R)-2-{N-(Indan-2-yl)-N-((2R)-1-cyclohexyloxycarbonyl-2,3-dihydroindole-2-carbonyl)-glycyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

16. Compounds of Claim 1 or pharmaceutically acceptable salts thereof, wherein:

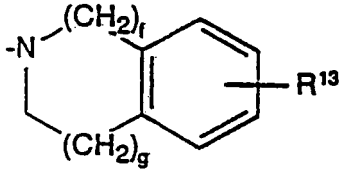
A is  XXXV

(II where R^2 is H and ⎯⎯ is a double bond),

or an N-terminally blocked α-amino acid residue containing an aromatic side chain; the N-terminal substituent is selected from R^2;

B is  XXIII

(X where c = d = e = zero)

C is  XXXVI

(XV where R^{14} and R^{15} are H, h = 0)

and wherein:

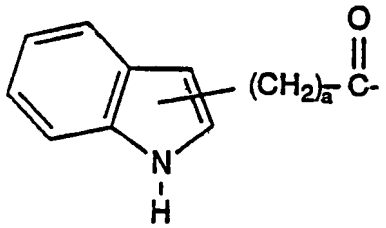
R^6 and R^7 are independently H or CH_3;

R^{22} and R^{23} are independently H, alkyl (C_1 - C_8, linear or branched), $-(CH_2)_o-R^{27}$ or $-(CH_2)_o-CO_2R^{27}$;

X^1 is H_2 or O

X_2 is H_2, O or S

17. Compounds of Claim 16 or pharmaceutically acceptable salts thereof, wherein:

A is  XXXVII

(XXXV where R^1 is H and X^1 is O)

or R^2-Trp;

R^2 is tert-butyloxycarbonyl, phenylcarbonyl, phenylmethoxycarbonyl;

R^6 and R^7 are H.

R^{13} is H.

18. The following particular compounds within Claims 16 and 17 or pharmaceutically acceptable salts thereof:

Example No.

110 1-{*tert*-Butyloxycarbonyl-tryptophanyl-leucyl}-2,3-dihydroindole.

111 1-{(2S)-2-(*tert*-Butyloxycarbonyl-tryptophanylamino)-hexanoyl}-2,3-dihydroindole.

112 1-{(2S)-2-(3-Indole-3-propanoylamino)-hexanoyl}-2,3-dihydroindole.

113 1-{*tert*-Butyloxycarbonyl-tryptophanyl-phenylalanyl}-2,3-dihydroindole.

114 1-{(2S)-2-(*tert*-Butyloxycarbonyl-tryptophanylamino)-4-phenylbutanoyl}-2,3-dihydroindole.

115 1-{*tert*-Butyloxycarbonyl-tryptophanyl-(β-O-benzyl)-D-aspartyl}-2,3-dihydroindole.

116 1-{*tert*-Butyloxycarbonyl-tryptophanyl-aspartyl}-2,3-dihydroindole.

Example No.

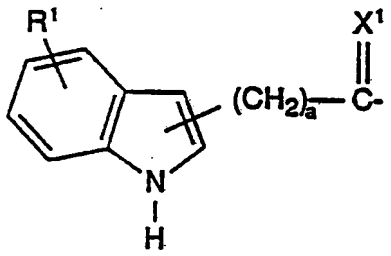
117 1-{*tert*-Butyloxycarbonyl-tryptophanyl-(γ-O-benzyl)-glutamyl}-2,3-dihydroindole.

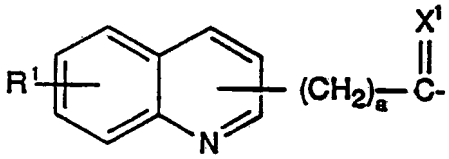
118 1-{*tert*-Butyloxycarbonyl-tryptophanyl-glutamyl}-2,3-dihydroindole.

119 2-{*tert*-Butyloxycarbonyl-tryptophanyl-D-phenylalanyl}-1,2,3,4-tetrahydroisoquinoline.

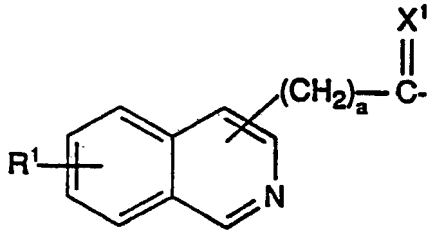
120 2-{(2R)-2-(*tert*-Butyloxycarbonyl-tryptophanylamino)-4-phenylbutanoyl}-1,2,3,4-tetrahydroisoquinoline.

19. Compounds of Claim 1 or pharmaceutically acceptable salts thereof, wherein:

A is  XXXV

 XXXVIII

(IV where R^2 is absent and ═══ are double bonds)

 XXXIX

(V where R^2 is absent and ═══ are double bonds), or R^2-Trp;

B is XXIII;

C is XV;

D is absent, Gly or β-Alanine;

and wherein:

R^2 is tert-butyloxycarbonyl, phenylcarbonyl or phenylmethoxycarbonyl;

R^6 and R^7 are independently H or CH_3;

R^{13} and R^{14} are H;

R^{15} is $-(CH_2)_i-CO-D-R^{18}$;

R^{18} is -OH, alkoxy (C_1 - C_3, linear or branched), $NR^{24}R^{25}$;

R^{22} and R^{23} are independently H, alkyl (C_1 - C_8, linear or branched), $-(CH_2)_o-CO_2R^{27}$, $-(CH_2)_o-R^{27}$ or $-(CH_2)_o-O-(CH_2)_p-R^{27}$:

a is 0 or 1
i is 0 - 2
X^1 is O, H_2 or S
X^2 is O or H_2

20. The following particular compounds within Claim 19 or their pharmaceutically acceptable salts:

Example No.

121 Ethyl (2R)-1-{*tert*-butyloxycarbonyl-tryptophanyl-leucyl}-2,3-dihydroindole-2-acetate.

122 Ethyl (2S)-1-{(2S)-2-(*tert*-butyloxycarbonyl-tryptophanylamino)-hexanoyl}-2,3-dihydroindole-2-carboxylate.

123 (2R)-1-{Indole-2-carbonyl-phenylalanyl}-2,3-dihydroindole-2-acetic acid.

124 (2R)-1-{(2S)-2-(Indole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetic acid.

125 3-{(2R)-1-{(2S)-2-(Indole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-yl}-propanoic acid.

126 (2R)-1-{(2S)-2-(5-Fluoroindole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetic acid.

127 (2R)-1-{(2S)-2-(5-Chloroindole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetic acid.

128 (3R)-2-{(2S)-2-(Indole-2-carbonylamino)-4-phenylbutanoyl}-1,2,3,4-tetrahydroisoquinoline-3-acetic acid.

Example No.

129 N-{(2S)-1-{(2S)-2-(Indole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-acetyl}-glycine.

130 3-{(2S)-1-{(2S)-2-(Indole-2-carbonylamino)-4-phenylbutanoyl}-2,3-dihydroindole-2-carbonylamino}-propanoic acid.

21. A medicinal composition comprising a compound or a salt thereof as defined in any of claims 1 to 20.

22. The medicinal composition of claim 21, which acts as a CCK-A, CCK-B or gastrin receptor antagonist or agonist.

23. The medicinal composition as defined in claim 22, which is a drug for the treatment of diseases or conditions induced by abnormality in a physiological function controlled by gastrin, including gastric and duodenal ulcers, gastritis, reflux esophagitis, gastric, colonic and other gastrin sensitive cancers, and Zollinger-Ellison syndrome.

24. The medicinal composition as defined in claim 22, which is a drug for the treatment of diseases or conditions induced by an abnormality in the physiological function controlled by the central CCK-B receptor, including anxiety, psychoses, Parkinson's disease, Tourette's syndrome, Huntingdon's chorea, disturbed appetite regulation and pain (including the treatment of pain by potentiation of opiate analgesia).

25. The medicinal composition as defined in claim 22, which is a drug for the treatment of diseases or conditions induced by abnormality in a physiological function controlled by the CCK-A receptor including disturbed appetite regulation, pancreatitis, pancreatic cancer, disorders of gastrointestinal motility (including irritable bowel syndrome), and gall bladder dysfunction.

26. A method of making a compound of the structure A-B-C as set out in any preceding claim wherein reactants giving the residues A, B and C are combined sequentially to form the compound.

27. A process for the production of the novel compounds of any of claims 1 to 20 described by the general formula A-B-C (claim 1), which comprises linking the sub-unit A to B-C, via an amide bond, particularly by HOBt/WSCD or bis (2-oxo-3-oxazolidinyl) phosphinic chloride mediated couplings.

28. A process for the production of the novel compounds of any of claims 1 to 20 described by the general formula A-B-C (claim 1), which comprises linking the sub-unit A to B-C, via a urea linkage, particularly by reacting the free amino terminus of B-C with the appropriate isocyanate.

29. A process for the production of the novel compounds of any of claims 1 to 20 described by the general formula A-B-C (claim 1), which comprises linking A-B to sub-unit C, via an amide bond, particularly by bis-(2-oxo-3-oxazolidinyl) phosphinic chloride mediated coupling.

30. A process for the production of novel compounds of any of claims 1 to 20 described by general formula A-B-C (claim 1), which comprises functional group manipulation of compounds A-B-C prepared as described in any of claims 26 to 29, including the hydrolysis of carboxylic esters to carboxylic acids, the removal of amino blocking groups, and the replacement of amino or carboxyl blocking groups with other blocking groups.

31. A method of preparation of a medicament for therapy by CCK-A, CCK-B or gastrin receptor antagonism or agonism, in particular for the diseases or conditions set out in any of claims 23 to 25, wherein a compound as defined in any of claims 1 to 20 is associated with a pharmaceutically acceptable diluent or carrier.

32. A method of therapy by CCK-A, CCK-B or gastrin receptor antagonism or agonism, in particular for the diseases or conditions set out in any of claims 23 to 25, wherein an effective amount of a composition according to any of claims 21 to 25 is administered to a person in need of such therapy.

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